Investing in our future
The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Tenth Board Meeting
Geneva, 21-22 April 2005

GF-B10-9
Annex 4

Portfolio Management and Procurement Committee Meeting
Geneva, 15 March 2005

MSH Europe
Renforcer les Programmes de Santé dans le Monde

Global Fund Policy on Quality Assurance for Pharmaceutical Products

Procurement of single and limited source pharmaceuticals

I. FINAL DRAFT

March 2005

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INTRODUCTION

1) Background

The current procurement policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) specifies certain conditions governing GFATM grantee ability to purchase single and limited source pharmaceutical products. For these products, the GFATM Board determined that quality assurance is particularly important. As part of its early deliberations on the GFATM procurement policy, some Board members were concerned that many recipient countries National Drug Regulatory Authorities (NDRA) may not have the technical capacity and resources to carry out necessary quality assurance. Consequently the Board adopted the following quality assurance requirement as part of the procurement policy:

"Provided products are accepted by the NDRA of the Recipient Country, to be eligible for purchase with Fund resources, any single or limited source product (that is a medicinal product for which there are not publicly available quality assurance standards, analytic methods and reference standards) must:

Option A - *Have been found acceptable to the UN procurement quality and sourcing project (also known as the WHO prequalification project) or*

Option B - *Have been authorized for consumption in their country by a stringent[1] regulatory authority or*

Option C - *Have been authorized by the NDRA in the Recipient Country"*

Option C was to have expired on December 31, 2004. At its November 2004 meeting, the GFATM Board extended this date to 31 April 2005 and asked that WHO undertake additional analysis on the experiences related to date with the use of Option C.

2) Objectives of the Study

The current study aims to

1) Review the experience with Option C to date
2) Identify the consequences of the expiry of Option C (supply, prices, quality, selection of products and rational use)
3) Identify the main procurement issues raised by the scaling up of global activities
4) Propose procurement options and scenario analysis

3) Methodology

The consultant worked closely with several WHO Departments and Offices in collecting data and analysis including the Office of the Assistant Director-General for HIV, TB and Malaria; HIV Department AIDS Medicines and Diagnostic Service; Rollback Malaria Department and RBM Partnership Malaria Medicines and Supply Service; Stop TB Department, Global Drug Facility and the Department of Medicines Policy and Standards. The team also worked closely with the GFATM Secretariat. The methodology used included:

- Assessment of the available information at the Global Fund, WHO, UNICEF, World Bank, IDA, Crown Agents, Mission Pharma and other procurement agents.
- Analysis of available information on procurement financed by the Global Fund.

[1] Stringent has been defined as an authority either belonging to the International Conference on Harmonization of technical requirements of registration of pharmaceuticals for human use (ICH) or to the Pharmaceutical Inspection Cooperation Scheme (PICS). **See ANNEX 1 for list of countries.**

- Consultation with suppliers, procurement agents and international stakeholders on current and future procurement issues.
- Analysis of the issues and scenario preparation.
- Draft recommendations to WHO and the Global Fund.

4) Original rationale for Option C and current concerns

During the initial discussion of the GFATM procurement policy some stakeholders had concerns about counterfeit and low quality products, whereas the WHO prequalification project was just beginning, and that many countries were concerned that Options A and B might be too restrictive. As a result of non-consensus, Option C was kept as a procurement possibility for GF grantees when the GF was launched. Other stakeholders were advocating for countries to be able to use their NDRAs and were concerned over impact on price and availability given a very limited supply of these types of products. The result was the compromise on time limits for Option C as noted above.

The quality of a pharmaceutical product can be defined in several ways and some stakeholders hold different views on the concept of "sufficient quality". Because it is essential that all patients supported by the GF have access to quality products, the definition here below has been adopted in the study.

A high quality drug is one that provides guarantees of efficacy and safety, is manufactured in a facility that fully abides by Good Manufacturing Practices (GMP), is compliant with quality specifications for starting materials and finished dosage forms (quality and purity), is bioequivalent to the originator product (to prove that a generic product is therapeutically interchangeable with the originator) and is subject to all necessary manufacturing and quality control measures.

Option C theoretically widens the options for procurement by countries supported by the Global Fund by increasing the number of potential suppliers. More suppliers normally lead to greater competition and lower prices. Studies undertaken by various analysts and in particular the price comparison made by IDA between "Option A or B" products and "Option C" products show that the potential for lower prices exists through procurement under Option C. However, this comparison is only fair provided the products are of proven similar quality, which is not well documented for products purchased to date under Option C.

For many products, the number of ICH/PICS registered or WHO prequalified suppliers remains low and price competition between them can be considered insufficient, regardless of the patent situation of the products. This remains true for several antiretroviral (ARV) and artemisinin combination therapies (ACT) products, especially second line products, in spite of efforts made by WHO to encourage companies to come forward and increase the pace of prequalification.

The limited number of quality-assured sources for specific drugs is due to several factors like absence of generic versions of certain products (e.g. some second line ARVs), absence of originators for certain generic Fixed Dose Combinations (FDCs) creating unusual challenges for generic companies willing to formulate these products (e.g. some ACTs), poor knowledge of pharmaceutical development among some companies, and time taken to do the development work including proper studies to prove the quality, safety and efficacy. It should be noted that even for well resourced generic manufacturers with know how, human and financial resources available, **it takes at least one year to develop a "new" generic drug.**

Some important factors that can contribute to slow progress in developing new sources of products meeting international standards is relative lack of incentive of local manufacturers to comply with international quality requirements. So far they all have had - with few exceptions - the possibility to sell their products locally to those who do not ask many questions about the

quality. The procurement processes that stick to requirements as laid down in Options A and B are in terms of money volume still relatively limited. In light of this, due appreciation should be given to those manufacturers who have invested in the quality of their products and made substantial progress. The paradox is that most stakeholders are increasingly in demand of good quality products but incentives to manufacture quality products are still very weak in many developing countries.

With several countries having started local production of ARV and many of those manufacturers still having not been cleared through the prequalification process of WHO, removing Option C would create a barrier to market entry and curb the effects of competition that their presence would have created. Of course this barrier would also avoid the procurement of potentially substandard products.

Limited experience with local product development, quality assurance and GMP manufacturing, lack of effective regulatory oversight, and limited resources may complicate the situation in countries where manufacturers are striving to manufacture antiretrovirals or other drugs locally. Many developing countries have yet to show that their local production can meet internationally recognized standards for quality assurance and control, and can offer prices that can compete with world market prices. In addition to the potential harm to patients who receive substandard drugs, there is the potential threat that use of low-quality drugs may contribute to the emergence of drug resistance and the eventual inutility of currently effective drugs should also be taken into consideration[2].

Retaining Option C could be looked from the point of view of favoring unfair competition (one can not compare price of products with sometimes dramatic differences in quality) as manufacturers with products not meeting international requirements for quality, safety and efficacy would still be eligible for projects using international donor money. This certainly could lead to a lack of motivation for further improvement of quality by developing country manufacturers.

It may be argued that, by promoting local registration of drugs used against AIDS, malaria and TB, Option C supports the concept of strengthening national drug regulatory capacity and[3] thus implicitly strengthens national drug registration authorities. So far, there is little evidence that this effect is happening in most developing countries that have used Option C. Moreover, all drugs irrespective of manufacturer must be registered locally thereby requiring strong national regulation.

Experience suggests that in many developing countries the NDRA still does not have the technical capacity to undertake all required tasks:

a) Some countries have granted registration of products that are inadequate, inefficient or dangerous:

Some countries in Africa have accepted in their markets fixed dose combinations of ARVs (e.g. Ginovir 3D case) which were dangerous. Several countries in Africa have registered fixed dose combinations of ARVs which were dangerous. With WHO's assistance some of these products were withdrawn but products of unknown quality and safety still remain widely circulated and in some cases, are still registered. One country has registered Artesunate + Mefloquin combination which is unnecessary and illogical in the national context[4]. In Asia some countries have accepted ARVs of dubious origin (claimed to be manufactured by Swiss company which is

[2] Source: Manufacturing of antiretrovirals in developing countries and challenges for the future. EB114/15, 114th Session, 2004, http://www.who.int/governance/eb/en/
[3] WHO Rapid Alert 110, www.who.int/medicines/organization/qsm/activities/drugsafety/orgqsmalerts.shtml
[4] Senegal: standard treatment guidelines for malaria, 2003.

not possible under Swiss law due to patent situation and the origin reportedly is a "post box" in Switzerland without any corresponding manufacturing plant in Switzerland)..

b) Some countries have granted registration to sub-standard products produced by manufacturers not meeting GMP:

Many manufacturers operating below Good Manufacturing Practices (GMP) standards and not having any substantive data about quality specifications manage to get their products registered and sold in some countries. A recent assessment conducted by WHO in several African countries revealed that between 50% and 90% of anti-malarials on the market did not meet international standards[5]. In addition, it is very difficult for a NDRA to refuse registration of medicines produced by a national company because of local political and economic pressures. In fact, in some countries Government owned factories may have the privilege to market their products without any registration. Moreover, recently WHO audited and assessed six manufacturers in one developing country upon request form the Government specifically for their capacity to manufacture ARVs. All six were found not to meet GMP standards and had very poor knowledge of proper pharmaceutical development of good quality products[6].

c) Many NDRAs in developing countries do not have enough qualified technical staff and laboratory capacity to conduct proper assessment of products during their registration, to carry out regular inspection of manufacturers and or to test and control the quality of products on the market[7]. In some countries regulatory staff may have even conflict of interest as they are also involved in private business to compensate low salaries that do not motivate pharmacists to work for the public sector.

I - EXPERIENCE WITH OPTION C

The principal aim of the study was to assess the current and past country experience in using Option C. The team encountered several limitations to collecting data which are included in the following discussion.

1) The Information Gap

To date, there is no one single repository for procurement information in the GFATM or elsewhere concerning procurement done with GFATM financing. This is perhaps partially the result of the young age of the GFATM Secretariat, but the absence of a basic procurement tracking system is a critical gap that needs to be filled.

Information available at the Global Fund

There is currently no systematic recording of procurement undertaken with Global Fund grants. Local Fund Agents (LFA) clear the procurement plan submitted by the principal recipient but do not have the responsibility for aggregating and reporting details to the FPM when the procurement of pharmaceuticals and health products occurs. The procurement unit in headquarters sets the procurement procedures of the GF but does not receive the feedback on actual procurement information. Portfolio Managers usually have more procurement information but procurement tracking is not their current responsibility. The procurement unit would be a

[5] The quality of antimalarials: WHO/EDM, May 2003
[6] Source: WHO Prequalification Project.
[7] source: “Effective Drug Regulations: what Countries can do”, WHO/EDM, March 1999

good clearing house for procurement and supply chain information and this unit should develop the necessary management information system to implement this function.

A voluntary information system developed by the GF to capture value of procurement, quality, supply chain challenges, etc., called the Price Reporting Mechanism (PRM) has been made available to countries since 2004. So far, only 17 of the 49 countries that have procured ARVs have documented some (but not all) of their procurement details into the mechanism. The PRM contains at present no data from TB or malaria grantees on procurement of any medicines under their grants. This system needs to be strengthened and countries should be mandated to provide the complete info as a condition of the GF grant.

Countries using Price Reporting Mechanism

Source: Global Fund

Africa	***Americas***	***Eastern Europe***	***Asia***
Benin	Cuba	Estonia	Cambodia
Burundi	El Salvador	Georgia	China
Central African Republic	Haiti	Moldova	India
Côte d'Ivoire	Honduras	Serbia and Montenegro	Kyrgyz Republic
Ghana	Nicaragua	Ukraine	Mongolia
Madagascar	Peru		
Malawi			
Swaziland			

Partial Reports Received Through Procurement Agents:

Source: *UNICEF*

Africa	***Americas***	***Eastern Europe***	***Asia***
Guinea			
Togo			Indonesia

Source: *IDA*

Africa
Ethiopia

Information available from WHO

There no mechanism for reporting on GF financed global procurement to WHO, and regional essential drugs advisers who were contacted did not have data available to them. In WHO headquarters, several new information systems exist that are designed to capture data for the disease specific conditions. Systems include:

- AIDS Medicines and Diagnostic Service (AMDS) – collects information on HIV/AIDS medicines and diagnostics; forecasts needs but is just starting to collect information on procurement. AMDS has a good level of information on manufacturers and products.
- The WHO prequalification project has a data base of all products applied for prequalification (which is substantive) but due to the confidentiality can not make the data available in detail of products that have not yet met prequalification criteria. The

poorest quality products probably never have been submitted for prequalification by the respective manufacturer.

- Malaria Medicines and Supplies Service (MMSS) – is a clearing house on malaria medicines and supplies. It has information on manufacturers of malaria drugs and supplies. It provides information on sales of Coartem (which under the agreement with Novartis are all done through WHO for the public sector of developing countries) – but does not keep track of procurement. An information system is currently under development for this purpose and should become operational by mid 2005.
- GDF – the Global Drug Facility for tuberculosis keeps track of all procurement of TB drugs performed by its procurement agent (currently UNDP/IAPSO) but does not monitor other procurement activities.
- GLC – the Green Light Committee has comprehensive information on products procured for MDR – TB, which derives from the mission of the GLC. However, most of these products are not procured with GF money.

Information from Procurement Agents

Large international procurement agents such as IDA Mission Pharma and UNICEF[8] have established their own prequalification procedures and they procure from manufacturers which may correspond neither to Option A nor Option B[9]. They have established their own prequalification procedures to select suppliers and regularly inspect and supervise them. However, these requirements are in some respects less stringent than those used by WHO. Although the procurement agents interviewed expressed high regard for the WHO prequalification scheme, they consider that companies do not come forward to be prequalified quickly enough and that WHO standards may omit some manufacturers with reasonable quality. Some of the respondents complained that WHO puts too strong an emphasis on quality assurance of the manufacturing facility (use of complete GMP procedures) rather than quality control of the product (laboratory testing of finished products before delivery). However, another viewpoint is that laboratory quality control alone cannot guarantee medicines quality, safety and efficacy as these properties cannot be tested into the product but have to be built into it.

It has to be noted that several procurement agents do not require bioequivalence studies from their selected suppliers. The WHO prequalification scheme is more stringent in this regard (as are ICH/PIC "stringent" regulatory authorities).

IDA and UNICEF were able to provide full information on procurement performed by them with Global Fund financing. Mission Pharma could provide only partial information as they do not disaggregate procurement data by source of funding. Crown Agents could provide limited information but has performed very little procurement with GF funds. Because international procurement agents have strict prequalification guidelines, their information will not cover many of the manufacturers whose products were purchased under Option C. Nevertheless, because it was the only complete information, it forms an important part of the study.

Information from Country Procurement

With the assistance of the GF and WHO, procurement information was obtained from 5 additional countries: Uganda, Zambia, Chile, Ghana and Thailand (partial information only: see Annexes 4, 5 and 6).

[8] For ARVs, UNICEF uses WHO Prequalification to guide its procurement.
[9] This approach could be considered a subset of Option C in that the recipient country would still require product registration prior to delivery or waive this requirement.

Financial data

Based on the data we were able to review it is not possible to assess how much GF money has been spent in total on drug procurement.
This is because:

- Figures in grant agreements are only indicative.
- Although the procurement plan has to be approved before disbursements take place, countries often have had to change their roll out plans; therefore planned procurement figures are not reliable indicators of actual procurement.
- Disbursement authorizations do not single out precisely the use of funds of drug procurement.
- Finally, countries reporting through the Price Reporting Mechanism do not always list all the products they have purchased.

2) Procurement Approach of Other Funding Organizations

U.S. President's Emergency Plan for AIDS Relief (PEPFAR)
Under the U.S. President's Emergency Plan, procurement of ARVs has been limited to products that have been approved by the U.S. Food and Drug Administration, which until recently meant almost exclusively American and European source products. The recent introduction of the USFDA 'fast track" scheme promises to expand the options for procurement under PEP and also increase the number of companies eligible for GF procurement under Option B. The first FDA fast track approval (February 2005) was of Aspen's (South Africa) co-packed ARV combination. It is expected that more companies will seek and gain this fast track approval in the near future.

World Bank
For HIV/AIDS, the World Bank has a procurement policy which allows the equivalent of option A and Option B of the Global Fund. Option C is not totally ruled out but its use is subject to prior approval of the regional procurement adviser of the World Bank - and so far this option has not been tested

Global Drug Facility (GDF)
GDF has been established by the Stop TB Partnership to provide inexpensive TB drugs to developing countries either under a grant agreement or reimbursable procurement, primarily for multi source TB drugs. The GDF uses its own prequalification method that does not correspond directly to any of the three Global Fund options. During the latest GDF tender, only WHO GMP approved manufacturers were eligible and products were assessed based on a test product, by an expert committee including prequalification team. Only WHO approved products were not assessed, except for stability studies and were systematically eligible.

Other donors
Canada is establishing legislation allowing Canadian firms to manufacture PICS registered ARV generics for export to the poorest countries. The European Union is working on regulation changes to the same effect[10]. These approaches are likely to also widen the scope of products available for GF procurement.

National Procurement

[10] Already, Article 58 of the European Pharmaceutical Regulation provides the possibility of for EMEA to give a formal advice to WHO about products manufactured in Europe for marketing outside the E.U.

Countries such as Brazil[11] and Thailand finance most of their ARV procurement with their own budget, although Thailand also uses GF funds. The primary method of procurement they use is presumably equivalent to Option C.

3) Description of the various aspects of Option C

Option C permits countries to buy products they have registered whether or not the products meet the requirements of Option A or B.

Local manufacturers

The issue of local manufacturing in developing countries has surfaced as an important dimension particularly relevant for ARVs and to a lesser degree ACTs. With the easier granting of product licenses and the promise of international funds through the GF, a number of investors have set up plants in developing countries. For example, local manufacturing of ARVs is beginning or is underway today in the following developing countries: Angola, Argentina, Benin, Brazil, China, Colombia, Costa Rica, Ethiopia, Gabon, Guyana, India, Kenya Mexico, South Africa, Thailand, Zambia and Zimbabwe. Several local manufacturers in these countries have registered products outside their country of origin. Most of this manufacturing of ARVs is very recent 2004 or 2005 and sometimes has not even started yet (Zambia). The decision to invest in ARV manufacturing was based on the availability of GF money and the anticipation of the possibility to export to neighboring countries; these businesses will be hurt by the removal of Option C, especially if they are not able to apply for prequalification in the short term, but that may be a necessary side effect of efforts to ensure that only high quality products are purchased with GF support

Although there is evidence that some of the mentioned countries have bought ARVs with GF money, there is no data to show whether or not they used local producers. However it is imaginable that Argentina, India and Thailand have procured from their local manufacturers under Option C.

Moreover, when a license (compulsory or voluntary) is issued, there is no guarantee of the quality of the licensed product. When a license is issued, the recipient manufacturer is immune against patent litigation but quality may or may not be assured (it presumably would be more likely in the case of a voluntary license).

Ultimately, the quality of locally manufactured drugs depends solely on the know-how and capacity of local manufacturers to develop and manufacture quality products in a sustainable manner. It also depends on the national legal requirements and strength of the NDRA's technical capacity to enforce compliance and ensure and maintain compliance with GMP of local manufacturers.

Locally registered products produced abroad

Foreign manufacturers considered in this section are those that are offering their product in a developing country but are not based in that country. The companies discussed here are not eligible for Option A or B, but they have registered drugs locally in some recipient countries. For example:

- The manufacturer Mepha has registered Artesunate in 20 developing countries without being WHO prequalified. Only one other manufacturer of this product, Sanofi-Aventis, is prequalified by WHO.

[11] Brazil is not a grantee of the Global Fund.

- Sanofi-Aventis has registered its combination Artesunate plus Amodiaquin in 13 developing countries although this combination is not yet prequalified by WHO.
- Mcleods Pharmaceutical (based in India) has registered various non prequalified ARVs in Kyrgyz Republic.

Although many of the foreign products registered in developing countries come from developed nations with a stringent NDRA, it does not mean that they automatically have received the level of scrutiny of Option B. Indeed some products are manufactured "for export only", and thus may or may not have had stringent NDRA scrutiny (although they may have undergone scientific review but not full marketing review).

Conversely, some manufacturers will not register their product in most developing countries because the local market is too small and/or the procedures are too long and costly. This is the case for several TB products that may be allowed in countries under exception clauses (i.e. a registration waiver may be granted for Government treatment programs), and for tenofovir (TDF) recommended by WHO as part of rational second line therapy..

Supply of non-prequalified products by manufacturers who have other products and manufacturing sites prequalified

Some manufacturers have obtained prequalification for specific products manufactured at certain manufacturing sites. However, they also may manufacture other medicines for which they have no prequalification approval[12]. As it is not determined whether these other medicines are manufactured in the same GMP plant, with the same manufacturing process that was prequalified, these other products may or may not meet GMP standards. Examples of GF procurement include:

- Didanosine procured from Cipla in Peru in June 2004
- Efavirenz from Cipla in Peru in June 2004
- Indinavir procured from Ranbaxy in Honduras July 2004
- Procurement of Ritonavir plus Lopinavir from Strides (India) in January 2004 although Strides was not prequalified at the time and is now prequalified for lamivudine and lamivudine/stavudine (FDC) only.

It is important to note that Cipla and Ranbaxy have registered Stavudine 30mg and 40mg in Malaysia, which is a PICS country. Therefore, although the product is currently not available through Option A (Prequalification), it will presumably become available through Option B[13].

4) Who makes use of Option C?

Only anecdotal information could be obtained on Option C utilization during the study due to the lack of data available to GF. However, some countries that performed direct procurement (i.e. did not use a procurement agent and for which information was available) have used Option C. For these countries, some information has emerged:

- Ukraine is ready to finance future procurement from its own budget to keep the same suppliers (who are not eligible for Option A or B)
- The Kyrgyz Republic has registered products that are not prequalified by WHO and has reported on purchase using Option C through GF funding in the Price Reporting Mechanism;
- Some countries may be using Option C because of the strong position of their national manufacturers (such as Brazil or Thailand)

[12] In certain cases, the product may look the same but have a different composition than the prequalified product.

[13] This is particularly important in the light of difficulties of access to stavudine encountered in early 2005 from the originator of the product.

- The Congo increased the cost of imported products by compelling manufacturers to sell through a national agent.

Products supplied using Option C reported in the PRM

Generic Name (INN)	Therapeutic	Name of manufacturer	Country
ARTEMETHER	anti-Malaria	Kunming Pharma. Corp.	China
CAPREOMYCIN	anti-TB	Cheil Jedang Corporation	Peru
DIDANOSINE (DDI)	anti-retroviral	Cipla Ltd.	Georgia
		McLeods	Kyrgyz Republic
		Cipla Ltd.	Peru
EFAVIRENZ (EFV OR EFZ)	anti-retroviral	Cipla Ltd.	Cuba
		Cipla Ltd.	Georgia
		Cipla Ltd.	Moldova
		Cipla Ltd.	Peru
		Cipla Ltd.	Ukraine
		McLeods	Kyrgyz Republic
INDINAVIR (IDV)	anti-retroviral	Cadila	Peru
		Cipla Ltd.	Peru
		Cipla Ltd.	Haiti
LAMIVUDINE (3TC)	anti-retroviral	McLeods	Kyrgyz Republic
LAMIVUDINE (3TC), ZIDOVUDINE (ZDV OR AZT)	anti-retroviral	McLeods	Kyrgyz Republic
NELFINAVIR (NFV)	anti-retroviral	Diethelm Keller Co. Ltd.	Cambodia
		Cipla Ltd.	Cuba
		Cipla Ltd.	Peru
NEVIRAPINE (NVP)	anti-retroviral	McLeods	Kyrgyz Republic
RITONAVIR (R)	anti-retroviral	Strides	Cuba
RITONAVIR (R), LOPINAVIR	anti-retroviral	Strides	Cuba
		Alpharma	Serbia and Montenegro
SAQUINAVIR (SQV)	anti-retroviral	Cipla Ltd.	Cuba
STAVUDINE (D4T)	anti-retroviral	McLeods	Kyrgyz Republic
ZIDOVUDINE (AZT)	anti-retroviral	McLeods	Kyrgyz Republic

Option C might be deemed a reasonable option to purchase a few products which are not registered in ICH/ PICS countries and for which manufacturers do not wish to seek WHO prequalification (Options A and B do not apply). Such products include most of the drugs for MDR TB (kanamycin, ethionamide,[14]). However, it is unlikely that manufacturers of these products will seek registration in developing countries because the market is too small. And thus procurement through GLC will likely remain the only option.

[14] Source: Green Light Committee

Size of "Option C" use: present and future.

The lack of documentation cited above makes it difficult to quantify the magnitude of Option C procurement. However, studying GFATM data for procurement for 720 products in 22 countries (for which some procurement documentation was available), it was found that out of a total of $32.8m procured in ARVs only approximately $974,000 were spent using Option C. This is less than 3%. It must be emphasized that information was only available on some ARV procurement, and did not include TB or Malaria drug procurement for which Option C and other methods are more likely to be used. Also, it did not include data from countries such as Argentina or Thailand which are probably more likely to have used Option C.

Still it remains that overall Option C has not played a major role in procurement financed by the GF to date (in the countries for which the study team could access information).

Even if Option C were retained, it seems unlikely it would take a much bigger share of GF procurement funds in the future for the following reasons:

- For most developing country manufacturers of products for the three diseases targeted by the GF, a local domestic market alone is unlikely to be sufficient to sustain their business.
- The pipeline for prequalified firms and products is increasing regularly and more procurement will happen through Option A. With the introduction of USFDA fast track approval it is likely more sources will become available through Option B as well.
- As GF procurement scales up, large prequalified companies will be better placed to access API and increase their production than local manufacturers of small size and limited cash flow.
- Finally, the option will remain for countries (especially middle-income ones) to purchase local production with their own budget resources rather than GF finance.

As a final word of precaution, if Option C were to remain as is in the future the motivation for developing country manufacturers to comply with international standards through prequalification may weaken and cash flow from GF may start to support more and more low quality production.

5) The WHO Prequalification Project - Relevant Issues Identified in the Study

Many products marketed and needed in developing countries are not registered in ICH/PICS countries. This is particularly true for some malaria and TB drugs. In addition, because of patent laws, generics of HIV/AIDS products are often not available for registration in these countries unless the product is manufactured in the country. If Option C is to disappear, greater reliance on the WHO Prequalification scheme will be necessary for products that are not registered in ICH/PICS countries, although the FDA "fast track" approach and initiatives taken by Canada and the European Union will alleviate some of the burden. Therefore it is important to analyze issues relevant to GF procurement.

Manufacturers that do not wish to enter (or re-enter) the prequalification scheme

Several manufacturers of single and limited sources products that would potentially be eligible for GF funding have not expressed interest in acquiring WHO prequalification. There is a variety of reasons:

- Some companies which have a large local market and do not wish to export in the short to medium term (Brazilian manufacturers of ARVs).

- There are not enough incentives for many generic companies from developing countries to comply with international standards through prequalification as they still can sell their products without it;
- Some companies may have manufacturing practices close to the high standard demanded by WHO but do not have the cash flow that investments to reach prequalification would require.
- For some companies the prequalification is expensive and may not be perceived as being necessary (e.g., manufacturers of MDR TB drugs)
- A few companies that have gone through part of the prequalification process but cannot or do not wish to comply with all of the remarks they have received from WHO reviewers (Svizera is an example).
- Some companies have expressed concern about the confidentiality of their data. (Merck).
- Some companies do not see the necessity of submitting data to WHO when their products have already been approved by a stringent regulatory authority such as USFDA.

Another important factor is companies' willingness and motivation to submit to prequalification requirements, which can be effectively created through using financial incentives i.e. rewarding the pre-qualified products with orders from GF recipients.

Length of the prequalification process

The mean time for companies that present themselves to prequalification to be approved reportedly varies according to a number of factors. For a company whose product does not require additional corrective measures to be taken to complete studies (like stability studies or studies for bioequivalence) or to respond assessors questions, and provided the company's manufacturing unit complies with GMP, the mean time can be as low as 3 months. For a company which has never undergone prequalification review or approval by a stringent regulatory authority, the mean time can range from 6-18 months depending on the nature of corrective measures to be taken by the company. If Option C is removed, a grace period should be considered to give companies that so wish time to become prequalified. It should be noted however that as of September 2004, 142 product dossiers had been received by WHO for TB drugs and 243 for HIV/AIDS drugs by November 2004[15]. Although WHO keeps the "failure rates" confidential, it can be expected that the number of prequalified products will continue to increase steadily, if the project continues to receive adequate funding.

WHO's approach to quality assurance and quality control

The WHO Prequalification Project is mostly about verifying that products prequalified meet WHO standards for quality, safety and efficacy but it does not represent a form of "international registration". The WHO web site describes in detail the steps taken by the project in terms of quality assurance

However, quality control of the product before shipment to the purchaser is not included in the WHO prequalification as a routine requirement[16] (as WHO is not a procurement agent). However, WHO reports it is doing random sampling and quality control testing of prequalified products. Procurement agents that were interviewed during the study suggested that a process of laboratory control of samples from some batches should be set in place. This is what IDA, Mission Pharma, UNICEF, GDF and the GLC do.

[15] Source: Website of the WHO Prequalification Project
[16] WHO has issued norms and standards for prequalification of quality control laboratories.

WHO's capacity to scrutinize product manufacturing and product quality in all its complexities is limited. It is an accepted regulatory principle that less frequent quality control testing is needed for products for which manufacturing processes and quality assurance mechanisms have been fully scrutinized, starting from active pharmaceutical ingredients through the whole process until finished dosage form manufacture.

Costs of prequalification

The WHO prequalification process can cost a manufacturer anywhere from minimal expenses involved in compiling and sending "ready to go" documentation, to several hundred thousand dollars or more if the company has to invest heavily to meet GMP standards[17]. The cost to improve is often exaggerated as sometimes better compliance can be achieved with just proper training of staff which is relatively cheap. The cost of bioequivalence studies is considerable (ranging from 10 000 to 100 000 USD plus) and cost/benefit depends on volume. For high volume products the prequalification cost per dosage unit is relatively small considering all other costs involved. The cost to WHO is also important in terms of staff time and travel, payment, daily allowance and travel of national experts and inspectors working for WHO (involving developing country experts), laboratory quality control analysis and regular one week trainings provided to manufacturers and NDRAs. Insufficient funding of the WHO prequalification project could lead to a slow down in the overall number of new products added to the list and damage competition for GF procurement.

Status of Prequalification to date

The progress of the prequalification project varies according to the targeted disease.

Malaria

Only two products have been prequalified so far although WHO states that 26 product dossiers have been received. The lack of antimalarials is particularly important because malaria manufacturers tend not to register in ICH/ PICS countries where there is little or no market. Because of that, several countries have relied on Option C for purchase of ACTs even if the manufacturer was not proven to be in compliance with GMP. The major problem here is that under international recommendations 45 developing countries have changed their malaria treatment guidelines to ACTs although the manufacturing capacity and raw material availability for ACT was not there. As a result, difficulties with access to ACT will persist regardless of prequalification status until more manufacturers make ACTs available.

It should be noted that making alternate ACTs is not easy as there is no originator product (i.e. nothing to copy) which makes it much more challenging for generic manufacturers involved. In addition, in several cases, manufacturers of APIs are limited and starting materials for the production of APIs are scarce. However, the prequalification pipeline for these products is promising and it is expected that some alleviation of this problem will be seen during 2005 and 2006.

Tuberculosis

TB products were considered here as regards the fixed-dose combinations, which can be procured from a small number of sources. Individual TB drugs do not fall within the scope of this study. As of September 2004, eight products have been prequalified including two 4 FDC (fixed dose combinations). However, the main supplier of the GDF (which is recognized as an acceptable supplier to Global Fund grantees) was not prequalified by WHO (no longer true as-the GDF now supplies products from 3 manufacturers that are WHO GMP approved). And

[17] Examples of costs to companies may include upgrading buildings (ventilation, sterility), staff training, new equipment, establishment of new procedures, manufacturing process documentation etc

several of the WHO prequalified companies have refused to participate in the last GDF tender. In addition, none of the drugs used for MDR TB have been prequalified by WHO so far.

The TB drug manufacturers may lack incentives to apply for prequalification as they can sell their products well without complying with the same international standards for quality, safety and efficacy. In addition, it is estimated that the GDF supplies only 10% of the world's demand for TB products.

Finally, it is important to note that most MDR TB products are well defined in terms of quality assurance standards, analytic methods and reference standards. According to GF procurement rules, they would normally not belong to the class of products for which special procurement rules should apply. It is reasonable to keep them here, however, because of their strategic importance and the risk that TB resistance to these second line products would create for international public health.

HIV/AIDS

As of November 2004, 87 products have been prequalified most of which are ARVs. Most first line ARVs have several prequalified manufacturers. However, recent reports of shortages of ARVs sold by multi-national companies at preferential prices may create doubts about the capacity or willingness of some of these companies to achieve proper scale-up at least in the short term.

Conclusion of this section

In spite of the progress to date the list of companies approaching WHO for prequalification project is still not at a mature stage where fully developed competition can emerge. To arrive at that result, there is a need for

- More companies applying for prequalification;
- Adequate technical support to candidate companies so that the process becomes easier for them, without creation of conflicts of interest for WHO Prequalification;
- More capacity in the WHO prequalification project;
- Clear and credible statement of increased funding from Global Fund for drug procurement to create incentives for more companies to seek prequalification: so far, funding delivered by GF grants has not been of the magnitude to create sufficient economic incentives for many manufacturers of API and finished products to invest in quality meeting international standards.

As discussed above, the emergence of the USFDA fast track approval process will add additional companies to the international competitive mix, although it is likely that many of these companies will also be WHO prequalified.

6) Position of some stakeholders on Removal of Option C

International organizations

Contacts were made with World Bank staff during the study. According to these sources experience with procurement of single or limited source ARVs with World Bank financing remains small. The World Bank supports the WHO prequalification project and considers the Option C as an exception requiring a clearance from the regional procurement adviser. It is the perception of the Bank that removal of Option C will not have a significant impact. However there is an expressed belief that intellectual property issues will become more preoccupying than Option C (notably after the new Indian law) as most developing countries are not prepared for the administrative demands of the Cancun agreement.

Procurement agencies

As has been stated previously, most reputable international procurement agencies have their own prequalification mechanisms for suppliers which would presumably be a subset of suppliers currently eligible under Option C. Most consider that removing Option C immediately would create a difficult situation in some countries which rely on the GF to finance their drug purchases. They indicated however they believe that most of the suppliers they prequalify could also potentially become prequalified by WHO.

Country authorities

There has been no time during the study to interview developing country authorities. However, chances are that different countries will have different reactions. Groups with local manufacturing capacity (such as Thailand) may be/are more likely to be in favor of continuing procurement from their national suppliers; countries with prequalified manufacturers are less opposed to the removal of Option C. The countries most likely to be opposed to the removal of Option C are the ones that have recently developed a national manufacturing capacity but whose manufacturers have not obtained prequalification from WHO or approval from a stringent regulatory authority[18]. For these countries, removal of Option C will lead to the inability to use GF grants to buy from their local manufacturers.

NGOs

There was dialogue with several NGOs during the study. The main concern of NGOs with the removal of Option C is the risk of insufficient competition possibly leading to shortages, longer lead times for deliveries and price increases.

[18] Such countries include Angola, Gabon, Ethiopia, Kenya, etc.

II – POTENTIAL ISSUES WITH THE REMOVAL OF OPTION C

1) In terms of product availability

Concern has been expressed that without Option C, the remaining WHO prequalified and ICH/PICS approved manufacturers may not be able to supply the market generated by GF grants, especially in the context of a rapid scale-up of purchases[19].

Production capacity of manufacturers

Between ICH /PICS and prequalified manufacturers, it seems likely that the production capacity for finished formulation of ARVs is sufficient to cover the needs that a rapid scale-up would generate. Most of these companies have a capacity of several million tablets per day[20]. There may be some limitations though. For example some multi-national companies may not be able to increase to a large extent the production of medicines for developing country use in the short term: recent failures to deliver the full quantity of products ordered in Uganda and Zambia show that this problem is more than theoretical[21].

The CEO of Cipla indicated that his company could raise its manufacturing capacity up to 20 million tablets per day and other manufacturers also have large capacity for finished ARVs. The main limitations for manufacturers such as Cipla is the availability of starting material[22] (API) and lack of financial guarantees from the international community to buy drugs that are produced (an important element in the decision to scale up for manufacturers).

Insufficient manufacturing capacity to manufacture enough quality products, together with API shortage, seem to be the main factors behind the current shortage of the ACT artemether/lumefantrine (Coartem®). It does not appear that generic versions of the artemether plus lumefantrine will be available before the end of 2005. There exists production capacity for other ACTs that are under prequalification review. Some have been procured under Option C[23].

There doesn't seem to be shortage of production capacity for most TB products and the major issue is more that of price of API than production capacity, except for MDR TB drugs for which the risk of shortage of finished products could become an issue because of the rapid increase of demand and the limited number of suppliers.

Risks of product shortages

Drug shortages might eventually result from two factors that are difficult to evaluate: the lack of capacity or willingness of some companies to augment their production and the lack of API.

[19] So far, there has only been limited procurement of pharmaceuticals with GF grants. Recipient countries often have placed emphasis on planning, mobilization of local capacity and supply chain management before drug procurement. In addition, disbursement of GF funds has been slower than expected. It is therefore expected that the pace of drug procurement will increase rapidly in 2005-06.
[20] For instance, the new Aspen plant in South Africa will provide the company with an additional capacity of 5 billion tablets per year (source: Aspen).
[21] Bristol Myers Squibb and Merck have indicated that they might not be able to meet the scale up of orders of stavudine and efavirenz respectively in the short term.
[22] The CEO of Cipla indicated that making its 3 FDC product "combivir" available for 1 million patients would require 110 tons of lamivudine per year; 146 tons of nevirapine and about 30 tons of stavudine.
[23] Dafra has been selling artesunate plus SP in North Sudan and artesunate plus Amodiaquin in Mozambique

Given that data does not exist on the first issue, it is difficult to speculate about its probability. Some of the people interviewed during the study expressed concern that some multinational companies providing single-source products at a low preferential price might be willing to do so for limited quantities only and might be reluctant to increase their supply of low-margin drugs[24]. In the absence of substantial evidence (besides the current tension on stavudine[25] and efavirenz supplies), this risk can only be called theoretical. The team could not ascertain from the GFATM its pipeline necessary to understand potential future shortages. And in some cases multinational manufacturers are granting voluntary licenses that are intended to allow production of the products by the licensee, taking the pressure off the licensor.

Shortage of API is a more real possibility, especially for ACTs and ARVs for which the market may increase in a manner that cannot be predicted precisely. GF, PEPFAR and the World Bank have established financial disbursement plans but speed of implementation and actual disbursement and pharmaceutical procurement have often not corresponded to the initial plans. The rapid increase in demand for Coartem (and ACTs in general) is an example of this problem: new sources of API have to be found – additional cultures of Artemisia Annua, notably in East Africa – and a delay exists between the acceleration of demand and the availability of API. Such delays are likely to lead to shortages and price increases.

It can be feared that shortages of API may be "organized" by producers finding themselves in a position of strength (monopoly or oligopoly). Some experts already suspect that this happening with several APIs for TB products: given the large volume of drugs financed by GF, profits from such behaviors could be high. Some of the interviewees suggested that a prequalification process for API would be indicated to help regulate a steady supply of API in the long term. WHO has already started inspecting API manufacturers as part of the prequalification process and depending on resources may speed up the process. It should be noted that some API manufacturers have already been inspected and accepted either by US FDA or by respective EU authorities and WHO is not intending to duplicate the work but rather to complement it in areas where this is needed.

In terms of visibility, it is important to realize that API manufacturers are not subjected to the same international scrutiny of NGOs, advocacy groups and the public as occurs with final product manufacturers. Changing prices and quantities supplied is much easier and less risky for API producers in terms of public image than it is for final drugs producers.

Conclusion of this section

The evidence gathered during the study leads to believe that the combined manufacturing capacity in ICH/PICS approved companies and WHO prequalified companies could be enough to cover the needs generated by the scale-up of procurement within 2 years[26].

Increase in API production capacity would be useful. This can be obtained through the market (if API sales are profitable), subsidies, and eventual prequalification of API manufacturers that would provide a sustainable profitable market for prequalified firms and increase their public accountability.

[24] One of the main concerns is that companies might not take decisions of eventual additional investment to meet increased demand.
[25] On March 1st, 2005, WHO prequalified stavudine and stavudine/lamivudine from Strides (India).
[26] Some of the originators have signaled possible difficulties in covering short-term orders over the next 2 years for stavudine and efavirenz. Alternative manufacturers should be able to fill the potential gap, at least for procurement financed by the GF. All of them are not prequalified yet. For ACTs, it is expected by MMSS/WHO that the current shortage should last less than 2 years.

2) In terms of product prices

Comparison of Option C product prices with prequalified products prices

In September 2004, IDA prepared a study of the potential impact of removal of Option C on single and limited source pharmaceuticals[27]. In that study they found that a large number of ARVs were available from a single prequalified source. They also found that if they had to purchase from ICH/ PICS or WHO prequalified sources only and not use the specific IDA selected suppliers, overall prices of ARV would increase by more than 25%. It should be pointed however that IDA was using its own prequalified suppliers as a reference, not necessarily any of the companies that supplied under Option C

The IDA findings could be considered to be consistent with the fears of NGOs that decreased competition would lead to higher prices. Indeed removal of Option C may withdraw some manufacturers of lower-priced products from GF procurement. However given the relatively low percentage of procurement done to date through Option C it is not clear the impact would be significant. The theoretical risk that other manufacturers would increase prices in response to removal of Option C seems unlikely. Although they remain imperfect, existing price reporting mechanisms and price comparisons published by several organizations have made procurement prices public and widely scrutinized.

The removal of Hetero and Ranbaxy products from prequalification of ARVs in November 2004 had a wide impact on the availability of ARVs for GF financed procurement. Their probable re-approval for WHO prequalification in the near future should add additional comparatively inexpensive prequalified products.

The recent increase in price of TB products has happened independently of Option C (source: GDF). Price hikes of API for 3 FDC and 4 FDC have led to requests by GDF suppliers for renegotiation of GDF contracts. The cessation of production of API for TB drugs by Novartis has reduced the availability of some raw materials and given the opportunity to other API producers to be in a position of strength by removing a powerful competitor.

Scenarios of price evolution for major classes of products

ARVs

There are a large number of new manufacturers world-wide for first line ARVs, including 3 FDCs and several of them have applied for WHO prequalification. It is expected now that Aspen has received FDA fast track approval other generic manufacturers will apply for and receive approval. Therefore it can be expected that by the end of 2005, competition will have increased for these products which should lead to lower prices. The same does not apply yet to second line products. Generics of these second line products could potentially be manufactured in countries such as India as most of their patents date back to before 1995 (with the exception of tenofovir). The FDC products may fall under patent once the mailbox[28] is open.

[27] Quality assurance of single and limited source pharmaceuticals: Implications of current Global Fund policy by Marten Jan Brouwer, MBA, Bianca Kamps, Msc & Machiel Wiersdma

[28] Article 70.8 of TRIPS allows developing countries that do not have patent protection for pharmaceutical and agricultural chemical products upon entry into force of TRIPS to establish what is called a mailbox system for receiving and filing patent applications for these products. The purpose behind a mailbox system is twofold: (1) it allows inventors to file for patents and thereby establish priority dates that serve as evidence of the novelty of their inventions, (2) while allowing countries to defer the actual granting of patents for pharmaceutical and agricultural chemical products. After the passage of a specified period, a country must retrieve applications from its "mailbox" and review them for patentability.

In terms of ARV prices, there is a high level of scrutiny from several sources and companies tend to keep prices at the same level regardless of the country of destination when selling through GF financing. Analysis of available prices charged by multinational companies showed that only minimal variations (linked to the Incoterm used) could be found between sales to procurement agents and sales to developing countries.

First and second line ARVs

WHO recommends that in resource-limited settings a single first-line regimen should be identified for the treatment of the majority of new patients. This regimen would consist of 2 nucleoside analogs and either a non-nucleoside or abacavir, or a protease inhibitor. Zidovudine (ZDV)/3TC are the initial recommendation for a dual nucleoside analog with d4T/3TC, vs ZDV/ddI and ddI/3TC as possible alternatives. Efavirenz and nevirapine are recommended non-nucleosides, while recommended protease inhibitors include ritonavir-boosted PIs (indinavir, lopinavir, saquinavir) or nelfinavir. A second line regimen should be chosen to substitute first line regimens when needed (for toxicity or treatment failure).

Source: WHO HIV Department

The same applied to Cipla and Ranbaxy, the most used generic manufacturers in the sample of orders that was analyzed. Given the publicity made about their prices, the risk that they would change them if Option C was removed is extremely low: we would expect that no company would want to face the "public outcry" that would most certainly follow such a decision.

TB drugs

There are two different cases: TB and MDR TB. For TB the current pressure on API prices, which may be partly related to the increase of oil prices (as petroleum products often are used for fine pharmaceutical chemistry), is likely to increase prices of 3 FDC and 4 FDC in the medium term. However, the emergence of new manufacturers that have applied for WHO prequalification should help to limit the price hike.

For MDR TB, the end of the special agreement between Eli Lilly and WHO for capreomycin and cycloserin will very likely result in a major price increase. (Non prequalified alternative sources are on average 4 times more expensive). The small size of the market and its limitation to the GLC as a nearly single client does not favor competition. If the number of cases of MDR TB increases, prices are likely to go up: new manufacturers would find themselves negotiating prices in a strong position and the end of the low-price agreement with Eli Lilly would remove a cheap alternative.

Malaria

Since October 2004 the price of all artemisinin based products has increased because of the upsurge in price of raw material. In the short term, prices should remain relatively high[29]. But over time, increase in the cultivation of Artemisia Annua should lead to more availability of artemisinin base and the price of API should stabilize and even decrease, unless demand out paces the growth of raw material availability. In addition, ACTs composed of artesunate and amodiaquin cost 30% less that coartem and the wider use of the cheaper alternative could help reduce prices. In the much longer term registration of other alternative ACTs will eventually drive malaria treatment prices downwards.

[29] The price of artesunate which was $1200 per kilo in November 2004 has decreased to $1000 in February 2005 which proves that a sizable component of the recent price increase was purely speculative.

In the specific case of Coartem, Novartis has been providing its product to the public sector of developing countries through WHO at their stated cost under a special agreement. The increase of API prices and the rapid increase in demand has led Novartis to ask for a renegotiation of the current agreement to get a higher price and a funding commitment over three years.

However, the situation of monopoly of Novartis is likely to end soon. Several companies have required WHO prequalification for other ACTs (artesunate plus amodiaquin, artesunate plus mefloquin, artesunate plus SP) and at least one additional manufacturer plans to produce artemether plus lumefantrine by the end of 2005.

Conclusion of this section

Although price variations can be expected in the coming months, they will probably not be linked to the removal of Option C, with the exception of non prequalified ACTs. Until other ACTs than coartem become WHO prequalified or approved by an ICH/PICS authority, some sort of exception will remain necessary for many countries to access them (the issue of whether they are GMP manufactured remains an important unsolved problem). The likely price increase of TB products in the short to medium term is not linked to local registration and should not be influenced by Option C status.

For ARVs, the case is a little more complex. Because of public scrutiny and monitoring of prices, a significant price increase related to the removal of Option C can probably be ruled out. The IDA study, which rightly points at the potential loss of lower prices of ARVs if procurement is restricted only to Options A and B, is commenting on the effect on access to manufacturers prequalified by a procurement agent (and not always registered in the recipient country as mentioned in Option C). Furthermore, the price differences they pointed were in relation with three products mainly: didanoside, efavirenz and nevirapine oral solution. Enquiry with several generic manufacturers and review of the Prequalification Project pipeline showed that the issue identified by IDA should be resolved rapidly for didanosine and nevirapine oral solution (several products in the prequalification pipeline) but might stay for another year at least for efavirenz[30]. It remains to be proven that the price comparisons made by IDA correspond to products of an equal level of quality to products available through options A and B

In conclusion, removal of Option C should have little effect on the price of quality products manufactured in GMP facilities.

3) In terms of competition

Number of qualified manufacturers by category of products

At present, the number of WHO prequalified and ICH/PICS registered products remains too low for an effective price competition to happen for some product classes. The table below shows the number of manufacturers for some forms and dosages of ARVs and the number of ICH/PICs registered and WHO prequalified manufacturers. In some cases the prequalified manufacturer is also the only ICH/PICS approved producer and the product is in fact available from a single source only.

[30] In the case of efavirenz, the "conflict of norms" is apparent between IDA and WHO. IDA has sourced efavirenz procurement from CIPLA (for countries such as Peru and Ukraine) and considers the product of high and dependable quality. However, CIPLA estimates that it will take at least 6 months before it is able to make an application to the WHO Prequalification Project. In Kyrgyz Republic and Georgia, efavirenz and didanosine have been procured using Option C from Cipla and McLeods Pharmaceuticals.

Status of procurement for selected ARVs

ARV	Number of manufacturers (1) in the world	Number of ICH/PICS manufacturers	Number of WHO prequalified manufacturers (2)	Comment
Abacavir 300 mg tab	3	1	1	ICH/PICS manufacturer is also WHO prequalified
Didanosine 100 mg tab	8	1	1	ICH/PICS manufacturer is also WHO prequalified
Efavirenz 600 mg tab	3	1	0	
Indinavir 200 mg cap	3	1	0	Hetero expected to be "requalified"
Lamivudine 150 mg tab	13	1	3	
Nelfinavir 250 mg tab	6	1	1	ICH/PICS manufacturer is also WHO prequalified
Nevirapine 200 mg tab	10	1	3	
Ritonavir 100 mg cap		1	1	ICH/PICS manufacturer is also WHO prequalified
Ritonavir/Lopinavir 13,3/133,3 cap		1	1	ICH/PICS manufacturer is also WHO prequalified
Saquinavir 200 mg cap	2	1	1	ICH/PICS manufacturer is also WHO prequalified
Stavudine 30 mg cap	11	1	2	Hetero and Ranbaxy expected to be "requalified"
Tenofovir 300 mg tab	1	1	0	
Zalcitabine 0,75 mg	2	1	1	ICH/PICS manufacturer is also WHO prequalified
Zidovudine 100 mg tab	14	1	3	Hetero and Ranbaxy expected to be "requalified"

(1) from: "Sources and prices of selected medicines and diagnostics for people living with HIH/AIDS" June 2004
(2) from: WHO prequalification project web site.

E. Additional Information

Product manufacturer	***# of ICH/PICS Manuf.***	***# of WHO prequalified***
Efavirenz 200 mg	1	0
Lamivudine 300 mg	1	0
Stavudine 30 mg	3	1
Stavudine 40 mg	2	2

Possible evolution of the number of competitors by class of products

The pipeline of the WHO Prequalification Project is large and increasing steadily. As of end February 2005:

- 39 anti-malarials are in the prequalification process. All are artemisinin derivatives and 9 are ACTs
- 59 TB products are in the prequalification process. Among these products, 5 are 4FDCs and 10 are products for MDR TB.
- 57 are products for HIV/AIDS, of which 38 are ARVs. However, although several of the ARVs seek prequalification for a FDC, all belong to the category of first-line ARVs. The situation is likely to remain that of limited procurement options for second line products in the medium term.

The current “pipeline” is encouraging and it is likely that a significant number of new manufacturers and products will become WHO prequalified in the coming months. And as

mentioned, the recent approval by USFDA of Aspens fast track application yields hope that other companies will apply for an receive approval through this mechanism.

Conclusion of this section

The current list of WHO prequalified and ICH/PICS approved manufacturers is presently too short to allow an effective price competition for some critical products The size of the pipeline leads to believing that this should no longer be the case once several new manufacturers have cleared the steps of the WHO prequalification process and/or the USFDA fast track process.. However, given the length of the prequalification process, especially with manufacturers that have little experience of the stringent application of international standards, it can be estimated that full fledged price competition will not be seen for another 18 months.

For TB products, the GDF is expected to organize a new tender in the coming weeks. GDF is concerned about the apparent lack of interest of several manufacturers invited to compete, reportedly because international prices are very low. The new tender should help clarify the status of competition in 2005 resulting from recent API price changes.

4) In terms of quality

Short or long term improvement

There is little documentation available on quality issues reported with products purchased using GF grant finance. In particular, countries that have used Option C have not reported finding products of unacceptable quality and no publication has been made of evidence of clinical inefficiency or frequent mention of adverse reactions. There was no evidence that mechanisms were set in place to actively look for quality problems, so the absence of such reports does not mean that there were no problems with product quality

In the absence of such reports, it is difficult to make any strong statement on the quality of products procured under Option C. It should be mentioned here again that procurement agents such as IDA and Mission Pharma procure from selected suppliers that correspond neither to Option A not Option B and apply their own control mechanisms over the quality of the products they supply[31]. But their prequalification procedures can not be equated with Option C.

Given that several manufacturers[32] that have supplied medicines under Option C have tried but have not yet been able to clear the WHO Prequalification requirements, one can assume that the condition in which the products were manufactured or the extent of controls that were applied were not GMP-compliant. Without inferring that the products' quality was insufficient, it can be assumed that the risk of quality issues may be higher with these manufacturers than with the ones supplying under Option A or B.

Concrete evidence, based on documented inspection reports made by qualified inspectors, was provided by WHO experts consulted during the study that showed that some of the manufacturers mentioned above who supplied under Option C did not operate from a GMP facility and would need to invest to reach that level[33]. Their share of the documented GF procurement to date remains small, but scaling-up would only exacerbate this problem in the near future if these manufacturers are in fact not meeting GMP standards but were able continue to supply drugs if Option C were retained

[31] Neither procurement agent requires proof of bioequivalence, contrary to WHO.
[32] The WHO Prequalification Project keeps exact figures about companies that have not cleared the prequalification process confidential.
[33] In some cases, there was no need for substantial investment but rather better trained and qualified staff.

Removal of Option C would presumably only keep manufacturers with the highest standards of production eligible for GF funding. As discussed, this should not result in decreased access for patients. In the long term, the WHO Prequalification Project should attempt to contribute to a general improvement of the quality of HIV/AIDS, malaria and TB drugs across countries. More and more companies will receive technical assistance, advice, comments, recommendations, etc. from WHO and hopefully reach the stage where products can become prequalified. The WHO Prequalification Project has already helped some companies to reach a level of quality they did not have earlier[34], which gives them more capacity to compete in the international market place. With a larger number of companies prequalified coupled with expanded approvals under the USFDA fast track process, it can be estimated that within some years, all GF supported countries will be able to benefit from the supply of high quality products only at affordable prices

The issue of quality control before delivery

At present, reputable international procurement agents insist on systematic independent quality control of a sample of batches prior to delivery. This is a service they deliver as part of their overall procurement mission.

It is worth noting that one way to improve the quality of Option C products would be to test the quality of batches prior to delivery, but this is not necessarily practical in many of the countries that would be candidates to use Option C

Most countries that currently import ARVs without a procurement agent do not have the capacity to perform such controls: their quality control laboratory may not be equipped appropriately, their staff may not have been adequately trained, reagents may be missing, etc. In some cases (such as combination ARVs) sophisticated equipment and analysis methods are required.

For instance, in Côte d'Ivoire, the national control laboratories realized it was not equipped to test batches of products received through Global Fund financing. Its requests for funding from the MOH or the Central Medical Stores were not successful. The Abidjan faculty of pharmacy made punctual dissolution tests but could not control quality of imported ARVs on a routine basis, As a result, there is no quality control of products prior to delivery (source: D*ean of the Abidjan faculty of pharmacy*).

For TB, the GDF uses an external and independent quality control laboratory for batch release before delivery of TB products. The service contract for this laboratory is financed by the GDF budget[35]. A similar mechanism could be envisaged with GF funding[36]; alternatively, countries importing ARVs should include – as several have already done – a component of support to their NDRA and national quality control laboratory. In the absence of such control, the use of Option C is represents a higher risk, as it combines a "non stringent" control of manufacturers with the absence of control of the end products.

Conclusion of this section

Removal of Option C would presumably contribute to increasing the quality of products procured with Global Fund financing. Already companies based in non ICH/PICS countries have started integrating the fact that the prequalification process opens new market possibilities for them.

[34] One such example is the Indian company Strides.
[35] The GDF has issued two separate contracts for procurement and quality control.
[36] The WHO Prequalification Project has already defined the standards for quality control laboratories.

More companies are expected to apply for USFDA fast track approval. Overall the growth of the product pipeline is encouraging.

The WHO Prequalification team currently carries out random sampling and quality control testing of prequalified products, during the assessment process as well as after their prequalification and supply. However, quality control testing by the recipient country may complement the Prequalification process by building local capacity. Prequalification by WHO of quality control laboratories in Africa is expected to start soon with the aim to create a network of laboratories meeting essential criteria for good quality control testing.

If procurement from sources that do not correspond to Option A nor B is to happen, it should be only from documented GMP compliant facilities and the products should be subjected to quality control before delivery to decrease the risk of substandard drugs being procured with Global Fund financing.

5) In terms of treatment continuity/patient adherence

Lack of data on treatment continuity and adherence

Once patients have started a treatment regimen for TB (six months treatment) or antiretroviral therapy for AIDS (lifetime treatment), the main problem is the possibility of supply disruptions. It was showed, however that compliance could be increased when a number of drugs could be replaced by a fixed dose combination[37],[38]. It is not believed that a change of suppliers should lead to decreased treatment compliance or treatment failure, assuming the old and new products are therapeutically equivalent..

However, no information could be found on the effect of changes of treatment regimens in countries supported by the GF (one of the reasons may be that procurement of medicines has been relatively recent). Such data is largely absent from any treatment program and thus not linked to the source of funds. Even the temporary "de-listing" of some products from the WHO Prequalification list seems not to have led to documented treatment changes or interruptions with documented effects, although in the absence of data it is not possible to comment on the impact of that delisting.

The relative importance of drug procurement and drug distribution mechanisms systems on adherence

A more important threat to treatment continuity is the variable quality of the supply chain management and distribution systems in recipient countries. The risk of temporary stock-outs because of poor drug management is much more important for patient compliance and continuity of treatment than possible changes of supplier or presentation of the product. During interviews, several experts reported that many recipient countries often had difficulties channeling products (notably ARVs and anti-TB drugs) to peripheral care facilities without experiencing supply chain deficiencies.

Conclusion of this section

[37] Expanding role of co-formulations in the treatment of HIV infection: impact of fixed-dose combinations. Valenti WM, AIDS Read. 2004 Oct;14(10):541-3, 547-50.

[38] Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review : J. Connor; N. Rafter; A. Rodgers; Bull World Health Organ vol.82 no.12 Geneva Dec. 2004

Based on available data, removal of Option C is likely to have little effect on treatment continuity adherence. However, given the lead time to procurement, a "weaning transition period" may be useful to decrease this risk in countries that have made extensive use of Option C.

6) Economic consequences of oligopolies: raw materials, potential cartels, etc.

As has been stated higher, removal of Option C will decrease the number of eligible suppliers, at least in the short term in some countries, unless a transition period is allowed. Reducing competition usually leads to higher prices. However, in the case of GF products, many of which are subject to very close scrutiny by civil society and other stakeholders, the immediate risk of higher prices is probably related more to availability of raw material rather than finished products, provided adequate GFATM reporting systems are put in place.

"Delayed price reductions" may occur (in other words, prices may not drop as quickly as desired). As product prices for the critical drug products are widely publicized, general price increases are unlikely but the incentive for manufacturers to continue to reduce prices is low barring competitive threats, and they are implicitly encouraged to maintain the price status quo as long as new competitors do not reduce prices. The incentive to reduce prices is decreased by the fact that commercial margins are minimal on many products financed by the GF.

Shortages are another form of possible problem with insufficient competition that has been discussed earlier. Shortages related to lack of competition are generally not related so much to the drive to increase profits (since prices are effectively "capped" in this market) but are due more to the absence of incentives to proactively increase production capacity for products which may contribute very little – if not negatively – to the overall profit of the manufacturer. The introduction of new manufacturers remains a good answer to that situation[39] as new manufacturers bring additional industrial capacity and increase available volume of products, assuming that API is available.

The risk of increased prices (and artificial shortages) in case of oligopolies is much higher with manufacturers of raw material for GF single and limited source products. API manufacturers are not subject to the same level of international scrutiny as producers of finished drugs, and less liable to be hurt by international pressure. Shortages have already been experienced over the past months for artemisinin base, ethambutol and rifampicin. This is a risk that is difficult to alleviate, as oligopolies of manufacturers of API are created by the current "global procurement" environment.

Normally, drug manufacturers in a dominant position would exercise pressure on API manufacturers to reduce prices of raw material; however because scale-up for ARVs is rapid and API manufacturers are few, the latter find themselves in a stronger position. As an alternative, drug manufacturers may try to renegotiate tender prices (currently the case with GDF) if they can, reduce quantities to try to "regain the upper hand" or decide to take losses[40], which is not a sustainable situation.

[39] In the case of Eli Lilly, the answer from the company to its monopoly situation on cycloserin and capreomycin has been to help generic manufacturers to break their monopoly through technology transfer and free license. Eli Lilly, aware of the potential PR damage of product shortages, has helped to generate "competitors". This solution may not be available for products with a strong patent protection and another strategy of their originator.

[40] The situation of Novartis with coartem at the beginning of 2005 belongs to that category. Novartis was supplying WHO with coartem at a low price; however as the price of raw material increased and its availability decreased, this supply became a loss-maker. Novartis had to reduce the quantities manufactured (or "not meet the target quantities") and is currently trying to renegotiate the WHO price.

7) The issue of patents and related national legislation beyond 2005

Removing Option C may create a temporary reduction in the number of suppliers of products for HIV, malaria and TB but increased activity of the WHO Prequalification Project and programs such as the USFDA fast track process should open the market to suppliers having gained a "label of quality" in large enough numbers to create adequate competition (as evidenced by the size of the "pipeline"). As suggested by World Bank respondents, the impact of changes in the situation with international patents is less clear.

Under the TRIPS agreement, several countries that did not have a product patent system in place agreed to establish it in 2005. During the years 1995-2005, a mailbox of patent applications was created, and these applications will now start being reviewed. Although nothing is certain, several pharmaceutical products are believed to be included, and some of the new ARVs may fall into that category. Several of the largest countries producing generic ARVs are directly concerned with this issue as generic manufacturing and exporting of these ARVs would presumably no longer be allowed unless provisions were made for voluntary or compulsory licensing

At present – the content of the mailbox is still unknown - the effect on ARV availability for international trade is only potential and it is not possible to analyze the possible consequences of this situation. The questions are particularly serious in the case of Indian generic manufacturers, which represent a large share of the current WHO prequalified supply of ARVs and TB products.

In case of "emergency" or serious threats to public health, a compulsory license[41] may be granted to a company that will be able to manufacture the product and market it in its own country against payment of a license fee. Under the Cancun agreement on Implementation of paragraph 6 of the Doha Declaration on the TRIPS agreement and public health, a manufacturer belonging to a trade zone could export to other members of that same trade zone[42].

As noted earlier, some originator companies have granted voluntary licenses for patented products to firms located in developing countries. This trend may or may not expand in future years.

To what extent either voluntary or compulsory licensing will prove to be applicable and viable to solve potential access issues is unknown at this time, particularly since the nature and scope of these issues is unknown..

It is clear that only a few countries are ready to react to the changed patent situation and GF and WHO will need to provide advice and support to help recipient countries deal with the new reality.

III – OPTIONS / RECOMMENDATIONS

As this paper has identified, limitations on data and general experience using or needing "option C" creates an uncertain environment for policy making. In this regard, a set of options are provided for the PMPC's consideration. Underlying these should be a regard for ensuring the

[41] It is important to mention that voluntary licenses have become an important phenomenon.
[42] A condition to enforce that clause is that more than half of the members of that trade zone are "least developing countries".

highest possible level of quality while maintaining adequate supplies for scaled up action and product competition.

Based on limited data that did not include experience of some countries likely to have used Option C, particularly for TB drugs, the following is a summary of the findings:

- Although some countries have used Option C, it does not appear to have played a major role in procurement financed by GF (less than 3% of ARV procurement).
- The quality of products procured under Option C has not been documented.
- With the limited data, it is not possible to adequately estimate the degree of supply disruption that could result from closing Option C in countries currently using it.
- Overall GFATM procurement is at an early stage, with expected large increases in country demand in the near term.

Resolution of this issue area requires consideration of a set of tradeoffs:

1. The most important criterion in procurement is to ensure the quality of the product; accordingly, the board policy insists that the GF shall finance the procurement of quality assured products only. There are a large number of counterfeit and sub-standard products in the market, and National Drug Regulatory Authorities (NDRAs) of several countries do not have the technical or the human resources to test newer or complex molecules (such as antiretroviral (ARVs), second line TB drugs, artemisinin combination treatment (ACTs)), nor do they have the capacity to implement large scale quality assurance programs. In a recent assessment conducted by WHO, between 50% to 90% of antimalarials and more than half of ARVs did not meet international standards[43]. By keeping Option C open, there is a risk that substandard products become a real issue in several countries with possible consequences in terms of drug efficacy, adverse reactions and resistance build up. In addition, the perspective of the removal of Option C in April 2005 has led to an increased flow of applications to the WHO Prequalification Project and this trend should be encouraged.

However,

2. Removing Option C "bluntly" may have serious adverse consequences. It is important that the solution proposed for GF procurement keeps possible solutions for eventual shortages and to balance the need to supply products of the highest quality with that of leaving enough competition to ensure prices remain low. In the short term, as has been shown above, there is a risk that the immediate removal of Option C would not meet the latter demand. Any final decision on procurement should therefore include a transition period meeting the short-term issues. If not, the choice would be between a decision that might worsen short-term difficulties or one that would have to be amended again in the near future. At present there is a real risk of acute shortage for at least two products: ACTs and efavirenz.

The ACT issue can be addressed by allowing countries to tap alternative sources to Novartis' Coartem, notably other combination (artesunate + SP, artesunate + amodiaquin) that are not prequalified yet. Although the Prequalification Project's pipeline has several artemenisin derivatives, it will take some time before they become prequalified and transition solutions must apply through procurement from non prequalified products.

The case of Efavirenz is more difficult. Merck is the only ICH/PICS manufacturer and there is no manufacturer in the prequalification pipeline or prequalified. Procurement agents such as IDA have sourced Efavirenz from Cipla; however, this company has indicated to the team that it would not be ready to apply for prequalification before several months.

[43] WHO Medicines Strategy 2004-2007

To note that for Stavudine, Strides Arcolab was recently prequalified in addition to the originators product and other companies are in the final stages of prequalification. However, the risk of shortage will be more severe for PEPFAR financing, as BMS is their sole source, than for GF financing.

The example of these products shows that the risk of depending on a sole source is important and may lead to supply shortages. All products that are single-sourced are at the mercy of a technical problem with the manufacturer or its inability to scale-up production in relation to increased demand. However, it is important that alternative sources are of high quality and the Prequalification Project is the best tool to ascertain that international standards are maintained.

F. Options for proceeding

It is then reasonable to state that a transition period would be necessary, with policy options to consider a different approach to encouraging new entrants and competition, while maintaining high quality drugs. Provision must be made for products that are not yet prequalified or for which manufacturers may not seek prequalification. A smooth transition should finally take in consideration the risk of too many "single source" products and propose possibilities of boosting competition. The implementation of the 'quality-assured' board policy, however, would result in a new challenge—for several critical products there would be only a single supplier, and for some products there would not be any UN prequalified or ICH or PIC/S suppliers. For example, today, for first and second line ARVs, there are 30 out of 40 total number of products (different formulations/presentations, including paediatric formulations) with only a single supplier (either research-based or generic manufacturers); for ACTs, one product has one acceptable[44] supplier, while none of the other ACTs have an acceptable supplier. The risk of having single or in some cases even two suppliers is the potential lack of capacity of suppliers leading to longer lead times and shipment delays, monopolistic pricing, and more significantly, single supplier risk in terms of access.

The extension to Option C expires on April 30, 2005. Given the potential for short-term shortages with selected products in some countries, the GF should consider the following measures:

Establishing a "final position" is particularly difficult in the current context, when Option C is supposed to disappear in the coming month: such a position needs to balance the objectives of the short term and those of the long term. The main reason for the removal of Option C is that it presents the risk for countries with weak NDRAs that they could purchase substandard products because of their inability to assure and control quality, or resist certain pressures for accepting low quality products. This risk is real but there are opportunities to minimize it.

Moreover, special consideration is needed for those products that are not nationally registered, particularly for those that are not ICH/PICS approved or WHO Prequalified. Products such as some MDR TB drugs for instance are often not registered in ICH/PICS countries and their manufacturers may not enter the prequalification scheme. It is proposed that international procurement agents with well-established quality assurance systems procure them during an interim period. In the exceptional cases when this could not be done, it is proposed that the head of procurement of the Global Fund be asked to provide a clearance (as is the case with the World Bank).

Hence, the current report leads to a recommendation that a final position should include provision for transition measures.

[44] A product is defined as ***acceptable*** if it has been prequalified by the UN prequalification project or is registered for use in ICH or PIC/S countries

G. A special note on WHO Prequalification

The process of prequalification is not entirely in the control of WHO. Even if WHO manages its internal processes efficiently and adds additional technical and human resources, there are other factors that may cause delays, which WHO cannot influence. For example:

a) The small market size may not provide sufficient economic incentives for the manufacturers to produce the product or to invest further to meet some of the conditions of the UN Prequalification Project (e.g. second line antiretrovirals such as ddI, LPV/r, TDF, etc; second line TB drugs and all antimalarials)
b) Bioequivalence and other studies/documentation to ensure safety and efficacy can take 6-24 months to be completed and several of these are ongoing
c) There may not be an originator product for benchmarking and this requires the development of new techniques for comparisons, e.g. artemisinin derivatives/antimalarials and some fixed dose combination drugs, and paediatric ARV formulations.
d) Lack of stability data to determine the appropriate shelf life; these studies can take 3-9 months to be completed on an accelerated basis
e) Lack of data of active pharmaceutical ingredients (API) quality, impurities, degradation profile
f) Manufacturers that do not meet GMP requirements are required to upgrade which may take 6-12 months and requires significant investment of funds to comply; some manufacturers may decide not to invest and may not reapply

OPTIONS

H. Option 1 – Product-specific system

Description

This option focuses on individual products and the number of ICH/PICS or WHO Prequalified approved manufacturers. For each HIV, TB or malaria drug, a minimum of two ICH/PICS and/or WHO Prequalified manufacturers must be available. If so, products with only NDRA review and approval would not be eligible for GFATM funded procurement.

For products that have no acceptable suppliers (none or one ICH/PICS or WHO Prequalified), the following methodology will be used in selecting a supplier, and should be selected in this order.

a) Suppliers whose products are currently in the process of being prequalified and have successfully passed the GMP inspection or at least one dossier´s assessment, quality, or bioequivalence (the corresponding list should be published on a web site).
b) Suppliers or products found acceptable by established international procurement agencies based on assessment and inspections (Note: GFATM is working on further developing a list of prequalified procurement agents).
c) Supplies or products that are registered for use in the country that intends to purchase the product

The GFATM procurement manager, along with others such as the RBM Partnership Malaria Medicines and Supply Service manager, can use additional information from WHO, procurement agents, RBM and Stop TB Partnerships, etc to assess the aforementioned information.

Once an additional acceptable supplier has been identified (thereby meeting the threshold of two manufacturers for a product), GF grantees may only buy medicines from these suppliers. However, if there are capacity issues and supplier(s) are not able to provide the product(s)

within a reasonable period of time (for example, ready to ship within 90-120 days from the time of order, or within a period of time to avoid treatment interruptions in the country), the GFATM Procurement Manager can authorize grantees to buying products from alternative suppliers as per the order listed above. Additional mechanisms will need to be developed within the Secretariat for specific situations (e.g., if an emergency order is needed and the supplier is not able to provide in a month, but a non ICH/PICS approved or supplier of non-prequalified product is able to provide?).

The product list should be updated on ongoing basis and PRs, LFAs and other stakeholders should be informed of the new list of 'Acceptable' suppliers through web site and other means, if necessary. Careful attention to and support for implementation is required.
For countries currently using Option C-related products, a specific transitioning period as described in **Option 2** below would need to be further developed.

Special attention must be given to drugs, such as MDR TB, which have limited market size, some generic suppliers and ICH/PICS approved product suppliers exist, but neither want to invest in the facilities or the process to become prequalified because it doesn't make economic sense. Some governments, such as New Zealand provide financial incentives and subsidies to encourage more suppliers to participate.

Advantages:

- It broadens the supply to a minimum threshold of manufacturers of single and limited use products and efficiently addresses possible shortages in the near term;
- By keeping a large number of manufacturers eligible for GF procurement, it increases the odds that prices might decrease;
- It addresses the issue of products for which only one or no manufacturer has reached WHO prequalification
- In the longer term, it does not create adherence problems that would be generated by a shift from locally registered manufacturers to prequalified manufacturers.
- It creates a "push-pull" set of incentives for industry to be ICH/PICS or WHO prequalified
- It retains specificity for products for which the circumstances (e.g., market dynamics, approval status) differ and thus allow greater flexibility and rigor on a case-by-case basis.

Drawbacks:

- In the short term, it may give the impression that single product manufacturers who have invested into improving the quality of their products are not rewarded (at least until additional manufacturers are approved for the product in question)
- It favours "unfair" competition as those meeting international standards have to compete with those who have not (quality has its price and only competition can bring it down), until such time as the threshold is met.
- It relies partially on the capacity of NDRAs in recipient countries and they are often too weak to register products adequately;
- It may further delay procurement, notably in countries where authorities may wait until a manufacturer of their choice is registered to start procuring;

Option 2 – 1-2 year grace period

Description

It is anticipated that by the end of December 31, 2005, all the listed products will have one or more suppliers. The benefit of this option is that it would be much simpler to implement,

however the downside of this option is the delay in adopting a more stringent quality standard. Therefore, allow a one to two year grace or phase out period for countries that have already used Option C in procurements. During this period these countries would be allowed to continue procuring from the manufacturers that have previously supplied the country under Option C. However, the following conditions are suggested:

1. The manufacturer/supplier should apply for either (a) WHO prequalification or (b) registration in an ICH/PICS country or US FDA fast track approval, and
2. The drug products must pass quality control testing in an internationally recognized laboratory. The GF grant should support the costs of testing as required.

Options A or B will apply to all other drugs not previously procured under Option C. This measure may potentially minimize disruption to the country's short- to medium-term supply situation, while it also will motivate the supplier to apply for WHO prequalification or for registration in a country with stringent NDRA. The requirement for testing will address concerns over product quality. The duration of this phase out can be established on the basis of projected capacity of the manufacturers to develop the documentation and site conditions to meet the Option A or Option B requirements and the capacity of the competent authorities to conduct the evaluations.

On a case-by-case basis, GF should be able to authorize procurement of exceptional products that cannot be procured under Options A and B. However, these procurements must comply with quality assurance/quality control requirements, through one of the following mechanisms:

1. The procurement may be done through international procurement agents to be recognized by the GF. This will require an assessment of procurement agents' QA/QC standards and processes and the establishment of an accreditation or recognition mechanism.
2. The products that are procured directly by the recipient country and not through a procurement agent, must be assessed by an internationally recognized/accredited quality control laboratory.

This measure addresses exceptional cases of products that cannot be procured under Options A and B, but that may comply with GMP or quality testing standards.

Advantages:

- It broadens the supply to the largest number of manufacturers of single and limited use products and probably efficiently addresses possible shortages in the near term;
- By keeping a large number of manufacturers eligible for GF procurement, it increases the odds that prices might decrease;
- It addresses the issue of products for which only one or no manufacturer has reached WHO prequalification
- It ensures continuity of treatment and does not create adherence problems that would be generated by a shift from locally registered manufacturers to prequalified manufacturers
- A 2-year transition period should be enough for the current Option C suppliers to successfully apply for prequalification by WHO. After the end of the transition period, deliveries on signed contracts would happen but no further procurement would be allowed if they were not prequalified.

It must be stated though that the "adherence issue" is mostly theoretical as the quantities procured so far under Option C would not suffice to treat patients for a long period and future procurement might have led to a product change regardless of the procurement option selected.

Drawbacks:

- It "punishes" those manufacturers who have invested into improving the quality of their products and de-motivates manufacturers to comply with international standards
- It favours "unfair" competition as those meeting international standards have to compete with those who have not (quality has its price and only fir competition can bring it down)
- It relies entirely on the capacity of NDRAs in recipient countries and they are often too weak to register products adequately;

- It opens the door to new manufacturers (in particular local manufacturers) that may not abide by minimal quality standards but gained registration regardless;
- It may further delay procurement, notably in countries where authorities may wish to wait until a friendly manufacturer is registered to start procuring;
- It removes the incentive for manufacturers to seek WHO prequalification and improve their quality standards.
- Uncertain which procurement agent are consider as eligible, what is a registered supplier (eligible or simply registered)?

Option 3 - Procurement Agent clause

Description

One of the proposals tabled by IDA in their study was that when removing Option C, the PMPC might consider adding to Options A and B the possibility to procure from manufacturing sites that have been found to be GMP-compliant by WHO or by established international procurement agents.

Advantages:

- WHO is moving towards making positive GMP inspection results available anyhow through making WHO Public Inspection Reports (WHOPIR) accessible through its web site
- It limits the risks of low quality products by imposing elements of selection based on some quality, although not as stringent as the Prequalification Project's;
- It allows more competition and lower prices, as shown in the IDA study
- By keeping more manufacturers as potential suppliers, it helps fight against potential shortage issues
- It has been used with success by IDA, UNICEF, Mission Pharma and the GDF (which works through an international procurement agent, IAPSO).

Drawbacks:

- Procurement agents have potential conflict of interest as regards to quality assurance
- It reduces the incentive for manufacturers to enter the prequalification system
- Procurement agents operate very different and not harmonized quality systems - thus potentially different treatment of the same product by the different procurement agents
- Potentially de-motivates manufacturers to do more than GMP compliance
- It introduces the concept of GMP compliance checked by WHO. WHO already has a very heavy workload with the Prequalification Project and GMP compliance is only one part of it. It is unlikely that WHO would accept applications for GMP compliance certification only.
- International procurement agents use selection system that are close but not similar and possible discrepancies could be created
- Defining an "established international procurement agent" will be difficult and may be equivocal;
- It would create an obstacle for countries wishing to procure directly without having to pay a procurement agent's fees.

Selection by procurement agents is a potentially useful way of dealing with the procurement of products that still have not received prequalification and are not registered in ICH/PICS countries in case of removal of Option C. However, the question remains how much better is the procurement agents selection as regards to Option C.

Option 4 - Removal of Option C altogether

The advantage of this option is that the GF would adhere to the board policy, and would continue to assure highest possible standards of quality and provide an incentive to other manufacturers to participate in the prequalification process. The drawback would be the risk of not having access to any or sufficient products to supply countries. As indicated by WHO, the unavailability of medicines could further increase the risk of countries using poor quality or substandard products.

Removing Option C altogether is the option currently recommended by the Board of the GF. It would not require any decision from the PMPC.

Advantages

- It does not require a discussion at the Board to get into force;
- It increases quality standards for medicines procured using GF financing to the highest level;
- It provides a strong incentives for pharmaceutical companies to seek Prequalification by WHO and thus comply with international standards for quality, safety and efficacy;

Drawbacks

- It can generate short term shortages that would damage the credibility of the Global Fund (especially in the current context of difficulties by certain multinational companies to meet increased demand);
- It accepts single suppliers for a large amount of drugs with the consequence that decreases of prices become unlikely in the short term
- It leaves aside the procurement of a whole set of products for which there is no prequalified or ICH/PICS manufacturers: most artemisinin based products, several MDR TB products, etc.
- It will increase the pressure on the WHO Prequalification Project.

Recommendations

Recommendation 1. Preferred Option

Each of the four options has pros and cons and none is fully satisfactory. It is therefore necessary to find a solution that would combine the advantages of each option without generating the most serious drawbacks.

Given the tradeoffs between retaining some flexibility to respond to real issues and problems, avoiding shifting burden for exemptions to countries and the GFATM Secretariat, and all the while retaining incentives for companies to be approved by ICH/PICS and/or prequalified by WHO, ensuring GFATM procurement of high quality drugs, ensuring adequate supply and competition, and recognizing the variance of situations concerning individual drugs, we recommend consideration of option 1 (that includes elements of option 2 and 3 as well).

Recommendation 2. Monitoring and evaluation information needs

The data limitations encountered in this study underscores the need to effectively collect information for monitoring and evaluation purposes that will allow timely and more informed decision-making. It is suggested that the GF collect information on procurement from countries (either through LFAs or some other channel), and that this information be centralized and managed on an ongoing basis. It was the team's impression that a project was under way in 2003 to establish a procurement information system.

At minimum, the type of information reported should include the total procurement value conducted in country under GF funding, total procurement for health products and pharmaceuticals, total procurement of ARVs, ACTs, TB drugs (first and second line), and other

categories, as needed; total value of products distributed and dispensed (at least for the above three categories). For each procured product, the supplier and procurement prices, together with the relevant Incoterm, additional costs for freight and insurance, and quality control results as relevant. For each order, information collected should include lead time and service level. Additional information could include stock position and stock-out details. GF information systems should be modified to capture this data and the procurement team should be strengthened with additional human resources.

I. Recommendation 3. Support to WHO Prequalification Project

The expected increased volume of applications to the WHO Prequalification Project will require additional technical and financial resources. The Global Fund should consider supporting the WHO Prequalification Project financially over the next three to four years to ensure timely prequalification of additional suppliers.

J. Recommendation 4. Strengthening NDRAs

WHO conducts its prequalification inspection visits always with the involvement of staff of the concerned NDRA as observers (due to potential conflict of interest and different from WHO national standards). It also involves developing country assessors in the assessment of product dossiers (but never assessing the products manufactured in their home country). It is important that the NDRA be strengthened under the prequalification process. In particular, training in quality assurance is an important element of NDRA performance. The WHO prequalification team conducts specific-to- product group (ARVs, antimalarial and TB drugs) trainings for regulators and manufacturers (in 2005 two one week courses have been conducted already). Countries with local manufacturers should be encouraged to include such training and other forms of strengthening in their application to the Global Fund. Experience with support to NDRA by other donors has not been uniformly good.

K. Recommendation 5. Recommendations for WHO

Manufacturers may need technical assistance to meet the prequalification requirements, particularly those related to GMP and bioequivalence. Based on the experience with TB drugs, technical assistance can help them shorten the process, make appropriate investments and receive needed training to meet international requirements. It is important that WHO continue to provide such assistance.

WHO already provides support to countries on intellectual property issues and it needs to continue this support in the area of compulsory (and voluntary) licensing and preparation of both manufacturing countries and importing countries to implement the recommendations of paragraph 6 of the Doha Declaration, finalized in Cancun.

L. Potential financial impact of recommendations

The financial impact of these recommendations for the Global Fund budget cannot be calculated based on available data.

Annex 1

Countries with stringent regulatory authorities

Pharmaceutical Inspection Cooperation Scheme (PIC/S) participating regulatory authorities		
Australia	Greece	Portugal
Austria	Hungary	Romania
Belgium	Iceland	Slovak Republic
Canada	Ireland	Spain
Czech Republic	Italy	Sweden
Denmark	Liechtenstein	Switzerland
Finland	Malaysia	United Kingdom
France	Netherlands	United States
Germany	Norway	

International Conference on Harmonization (ICH) participating regulatory authorities
European Union member states
Japan
United States

Annex 2

Manufacturers of ARVs

Information based on AMDS (WHO) source and review of available procurement information

ARV	ICH/PICS	Prequalified	Other manufacturers
Abacavir	GSK	GSK	Cipla (India), ESCO (India), Ranbaxy (India), Richmond (Argentina)
Amprenavir	GSK	GSK	--
Didanoside	BMS	BMS	Aurobindo (India), Cipla (India), ESCO (India), Hetero (India), McLeaods (India), Ranbaxy (India), Far Manguihos (Brazil), Cristella (Brazil), FURP (Brazil, Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Funed (Brazil), Lifal (Brazil), Dosa (Argentina), Richmond (Argentina), Apotex Mexico (Mexico), Mchem (China), Shangai Desano (China), Zheijiang Huahai (China)
Efavirenz	Merck		Aurobindo (India), Cipla (India), Hetero (India), Mcleaods (India), Ranbaxy (India)
Ganciclovir	Roche	Roche	--
indinavir	Merck		Aurobindo (India), ESCO (India), Cipla (India), Hetero (India), Ranbaxy (India), Strides (India), Far Manguinhos (Brazil), Cristalia (Brazil), Funed (Brazil), FURP (Brazil), Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Lifal (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), GPC (Guyana), Cambodia Pharmaceutical Enterprise (Cambodia), Mchem (China)
Lamivudine	GSK,	GSK, Cipla, Strides	Aurobindo (India), ESCO (India), Emcure (India), Hetero (India), Intas (India), IPCA (India), McLeaods (India), Ranbaxy (India), Zydus Cadila (India), Far Manguinhos (Brazil), Cristalia (Brazil), Funed (Brazil), FURP (Brazil), Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Lifal (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), New GPC (Guyana), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), Samchully (Korea), GPO (Thailand), Mchem (China), Northeast General (China)
Lamivudine/ zidovudine	GSK	Cipla	Hetero (India), Ranbaxy (India), Aurobindo (India), Mcleods (India), Strides (India), Zydus Cadila (India), Far Manguinhos (Brazil), Cristalia (Brazil), Funed (Brazil), FURP (Brazil), Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Lifal (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), New GPC (Guyana), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), GPO (Thailand), Kimia Pharma (Indonesia), Mchem (China)
Lamivudine/ stavudine/ nevirapine	GSK	Cipla	Aurobindo (India), ESCO (India), Hetero (India), Intas (India), Ranbaxy (India), Strides (India), Richmond (Argentina), New GPC (Guyana), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), GPO (Thailand), Mchem (China)
Nelfinavir	Roche	Roche	Aurobindo (India), Cipla (India), ESCO (India), Hetero (India), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina)
Nevirapine	Boeringher Ingelheim	Boeringher Ingelheim, Cipla, Hetero	Aurobindo (India), ESCO (India), Emcure (India), Ranbaxy (India), McLeaods (India), Strides (India), Far Manguinhos (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), New GPC (Guyana), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), GPO (Thailand), Duopharma (Malaysia), Kimia Pharma (Indonesia), Mchem (China), Shanghai Desano (China), Zheijiang Huahai (China)

ARV	ICH/PICS	Prequalified	Other manufacturers
Ritonavir	Abbott	Abbott	Mchem (China)
Ritonavir/ Lopinavir	Abbott	Abbott	Hetero (India)
Saquinavir	Roche	Roche	Hetero (India), Strides (India)
Stavudine	BMS	BMS	Aurobindo (India), Cipla (India), ESCO (India), Emcure (India), Hetero (India), Mcleods (India), Ranbaxy (India), Far Manguinhos (Brazil), Cristalia (Brazil), Funed (Brazil), FURP (Brazil), Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Lifal (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), New GPC (Guyana), Apotex Mexico (mexico), Aspen (South Africa), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), Samchully (Korea), GPO (Thailand), Mchem (China), Northeast General (China), Shangai Desano (China)
Zalcibatine	Roche	Roche	--
Zidovudine	GSK, Combino	GSK, Combino, Cipla	Aurobindo (India), ESCO (India), Hetero (India), IPCA (India), McLeods (India), Ranbaxy (India), Samarth (India), Strides (India), Zydus Cadila (India), Far Manguinhos (Brazil), Cristalia (Brazil), Funed (Brazil), FURP (Brazil), Iquego (Brazil), IVB (Brazil), Lafepe (Brazil), Lifal (Brazil), Dosa (Argentina), Filaxis (Argentina), Richmond (Argentina), New GPC (Guyana), Apotex Mexico (Mexico), Aspen (South Africa), Cambodia Pharmaceutical Enterprise (Cambodia), Cheil Jedang (Korea), GPO (Thailand), Mchem (China), Northeast General (China)

Annex 3

Procurement of drugs for MDR TB

IDA Foundation has been contracted by WHO as the procurement agency responsible for the procurement and distribution of second-line anti-tuberculosis (anti-TB) drugs for treating patients with MDR-TB in the projects approved by the Green Light Committee (GLC). Once a project has been approved, the GLC secretariat provides an official letter to IDA specifying the quantities of drugs approved and facilitates contact between the project and IDA.

In line with its contract with WHO, IDA continuously negotiates the best possible prices for the drugs concerned and adds a 7% handling margin.

In addition, following an agreement between WHO and the manufacturer Eli Lilly, limited quantities of capreomycin and cycloserin are offered at a reduced price to GLC-approved projects.

WHO performs quality control with an independent laboratory (recommended by WHO) before each shipment; and for all products non-WHO approved and supplied as alternative when product under option B is not available. Costs are assumed by WHO.

Global Fund finance can only be applied to financing of MDR TB drugs following approval by the Green Light Committee.

MDR TB Drugs and Suppliers

Drug name	ICH/PIC suppliers		Suppliers in non ICH/PIC countries None are yet prequalified by WHO (under process) but all were approved by IDA		Drug Therapy Combinations
Capreomycin	Eli Lilly (USA and England)	Limited quota; There is special agreement with WHO to supply a certain quantity for 2 years at a special price of $1 per inj of 1gm normal price is more than $10 to the private sector; no other supplier has been identified	Cheil Jedang (Korea)	The product is being provided at $3.68	Use one of these injectables during the first 9 months +
Kanamycin		Have not been able to locate other PIC/ICH registered suppliers, although GLC believes others must exist	Panpharma (France)	Product registered for export only; supplied at $23.20 for 50 x 1 gm vials - potential sources in several countries	
Amikacin Inj		Innovator could supply, but has not been contacted, due a very limited demand	Gland Pharma (India)		
Cycloserin	Eli Lilly (Europe)	Limited quota; There is special agreement with WHO to supply a certain quantity for 2 years at a special price of $13.65 per 100 caps. No other supplier has been identified	Macleods (India)	$52.50 for 100 caps	Use this
Paser/Pas	Jacobus (USA)	Small company with limited production capacity;Product price is $47.60 for 30 x 4gm sachet (oral granules), no other supplier has been identified	Macleods (India)	Was supplying the product at $10 for 100gm; undergoing modifications on the formulation, can't supply until March 05	Use this
Ethionamide		Cannot locate a supplier	Macleods (India)	Price: $9.98 100 tabs 250mg; other suppliers should be available	Use one of these
Prothionamide	Fatol (Germany)	Fatol will supply in the future potential this product- price of $9,95/100 caps		Have located alternative source for this product like Lupin in India but no responsive. McLeods makes it, but doesn't export this product.	
Ofloxacin	Aventis (France)	Currently negotiating with Aventis for price, quantities, etc.	Brown and Burke (India)	Various suppliers exist; B&B price $4.46 for 100 tabs 200mg	Use this

Annex 4: Country data - Chile

Chile Procurement of Drugs through Public Tenders via UNDP

First Purchase

Drug	Supplier & Manufaturer	Volume (1)	Unit Cost FOB US$ (2)	Unit Cost CIF US$ (3)	Value CIF US$ (1x2)	Value CIF US$ (1x3)
1. STAVUDINE 40 MG X 60 tab (ZERIT)	Bristol-Myers Squibb	2 160,00	73,80	74,80	159 408,00	161 568,00
2. EFAVIRENZ MR 600 x 30 tab (Stocrin)	Merck Sharp & Dohme	2 400,00	126,00	126,80	302 400,00	304 341,00
3. NEVIRAPINE (NVP) 200 MG .X 60 CP (VIRAMUNE)	Boehringer Ingelheim	1 200,00	55,00	56,60	66 000,00	67 900,00
4. KALETRA vials of 180 tab (LOPINAVIR / RITONAVIR)	Abbot Labs	1 200,00	355,00	357,90	426 000,00	429 505,00
Subtotal					**953 808**	**963 314**
Second Purchase						
1. EFAVIRENZ (EFV) 200 MG, caja 90 caps	Merck Sharp & Dohme	1 400,00	126,00	130,83	181 440,00	188 395,00
2. STAVUDINE (D4T) 40 MG, caja 60 tab	Bristol-Myers Squibb	216,00	76,15	79,46	164,48	17 163,00
3. NEVIRAPINE (NVP) 200 MG caja 60 tab	Boehringer Ingelheim	2 208,00	55,00	56,65	121 440,00	125 083,00
4. DIDANOSINE (DDI) 400 MG, caja 30 tabs	Bristol-Myers Squibb	216,00	65,00	67,98	14 040,00	14 684,00
5. ZIDOVUDINE 300 MG + LAMIVUDINE 150 MG (AZT + 3TC) **COMBIVIR**, caja 60 tabs	GlaxoSmithKline	6 972,00	19,50	21,22	135 954,00	147 946,00
6. LAMIVUDINE (3TC) 150 MG caja 60 tabs	GlaxoSmithKline	2 160,00	5,70	7,00	12 312,00	15 120,00
7. ABACAVIR 300 MG + ZIDOVUDINE 300 MG + LAMIVUDINE 150 MG (ABC+ AZT + 3TC) **TRICIVIR**, caja 60 tabs	GlaxoSmithKline	1 392,00	102,00	106,19	141 984,00	147 816,00
8. ABACAVIR 300 MG, caja 60 tabs	GlaxoSmithKline	936,00	72,90	76,22	68 234,00	71 342,00
Subtotal					**691 853**	**727 550**
Total year 1 and 2 before UNDP Commision					1 645 661,00	1 690 864,00
Total year 1 and 2 after UNDP Commision						**1 741 590,00**

Annex 5: Country data – Uganda

PRODUCT	Strength	Basic Unit	Pack Size	Quantity	Unit cost USD CIPEBB	TOTAL COST USD CIP EBB	MANUFUCRURER	STATUS
1.D4T/3TC/NVP	40+150+200 mg	Tablet	60	32 592,00	13,23	431 172,60	CIPLA	Award made
2.D4T/3TC/NVP	30+150+200 mg	Tablet	60	136 321,00	12,42	1 693 597,58	CIPLA	ordered and delivered
3. AZT/3TC	300+150mg	Tablet	60	13 471,00	16,00	215 536,00	CIPLA	Award made
4. NVP	200mg	Tablet	60	6 062,00	5,24	31 734,57	HETERO	Award made
5.EFV	600mg	Tablet	90	7 409,00	26,98	199 894,82	CIPLA	Award made
6. D4T	40 mg	Tablet	60	2 857,00		0,00	BRISTOL MYERS SQUIBB	supply shortage, order pending confirmation of availabilty of supplies
7. D4T	30 mg	Tablet	60	4 854,00				supply shortage order pending confirmation of availabilty supplies
8. ddI	200mg	tablet	60	5 781,00		0,00	BRISTOL MYERS SQUIBB	supply shortage ,order pending confirmation of availabilty supplies
9. ddI	100mg	tablet	60	767,00		0,00	BRISTOL MYERS SQUIBB	supply shortage ,order pending confirmation of availabilty supplies
10. ddI	25mg	tablet	60	3 657,00		0,00	BRISTOL MYERS SQUIBB	supply shortage,order pending confirmation of availabilty supplies
11. kaletra	133.3/33.3mg	capsule	180	7 226,00	44,00	317 944,00	ABBOT	order witheld pending review of actual demand data. Slow movement of stock purchased with WB funding
12. 3TC	150mg	Tablet	60	3 561,00	5,70	20 297,70	Glaxosmithkline	Award made
13. AZT	300mg	tablet	60	3 843,00	10,75	41 312,25	CIPLA	award made
14. AZT syrup	10mg/ml	bottle/200ml	1	20 140,00	4,04	81 365,60	CIPLA	award made
15 3TC syrup	10mg/ml	bottle/240ml	1	20 140,00	4,84	97 477,60	CIPLA	award made
16. NVP syrup	10mg/ml	bottle/240ml	1	20 140,00		0,00	Boheringer	awaiting submisson of quotation
17. Nelfinavir	250 mg	tablet	270	852,00	75,72	64 513,44	ROCHE	award made
		TOTAL				3 194 846,16		

It is interesting to notice in the table here above that Uganda already experienced problems of difficulty of a multinational company to supply ARVs: it this case, shortage of didanosine and stavudine to be supplied by BMS.

Annex 6: Country data – Zambia

DEC 2004 PROCUREMENT BY ZAMBIAN MOH		
MANUFACTURE	**DRUG**	**USD**
GlaxoSmithKline Export Limited	Abacavir 300mg tabs/PAC-60	145800
GlaxoSmithKline Export Limited	Abacavir oral sol. 20mg/ml/BOT-240ml	75544
Ranbaxy Laboratories Ltd.	d4T/3TC 40+150mg tabs/PAC-60	29220
Cipla Ltd.	d4T/3TC/NVP 40+150+200mg tabs/PAC-60	943200
Bristol-Myers Squibb Sarl	Didanosine 100mg tabs/PAC-60	10633,5
Merck Sharp & Dohme B.V.	Efavirenz 600mg tabs/PAC-30	399000
Merck Sharp & Dohme B.V.	Indinavir 400mg caps/PAC-180 pb	78000
Cipla Ltd.	Lamivudine 150mg tabs/PAC-60 gp	63160
Hetero Drugs Ltd.	Lamivudine 150mg+Zidovudine 300mg/PAC-60	420315
Cipla Ltd.	Lamivudine oral sol. 10mg/ml/BOT-100ml	51840
F. Hoffmann-La Roche Ltd.	Nelfinavir 250mg tabs/PAC-270	69063
F. Hoffmann-La Roche Ltd.	Nelfinavir 50mg/g powder/BOT-144g	185156
Cipla Ltd.	Nevirapine 200mg tabs/BOX-60	227500
Boehringer Ingelheim GmbH	Nevirapine oral susp. 10mg/ml/BOT-240ml	301875
F. Hoffmann-La Roche Ltd.	Saquinavir 200mg [hard] caps/BOT-270	50400
Bristol-Myers Squibb Sarl	Stavudine 30 mg caps/PAC-56 pp	23791
Hetero Drugs Ltd.	Stavudine 30mg caps/PAC-60	8796
Bristol-Myers Squibb Sarl	Stavudine 40 mg caps/PAC-56 pp	12600
Hetero Drugs Ltd.	Stavudine 40mg caps/PAC-60	10734
Bristol-Myers Squibb Sarl	Stavudine oral sol. 1mg/ml/BOT-200ml	47880
Cipla Ltd.	Zidovudine 300mg tabs/PAC-60	31500
Cipla Ltd.	Zidovudine oral sol. 10mg/ml/BOT-100ml	73440
Total procurement by Zambian MOH		**3 259 447,50**

Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health

Decision of the General Council of 30 August 2003 *

The General Council,

Having regard to paragraphs 1, 3 and 4 of Article IX of the Marrakech Agreement Establishing the World Trade Organization ("the WTO Agreement");

Conducting the functions of the Ministerial Conference in the interval between meetings pursuant to paragraph 2 of Article IV of the WTO Agreement;

Noting the Declaration on the TRIPS Agreement and Public Health (the "Declaration") and, in particular, the instruction of the Ministerial Conference to the Council for TRIPS contained in paragraph 6 of the Declaration to find an expeditious solution to the problem of the difficulties that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face in making effective use of compulsory licensing under the TRIPS Agreement and to report to the General Council before the end of 2002;

Recognizing, where eligible importing Members seek to obtain supplies under the system set out in this Decision, the importance of a rapid response to those needs consistent with the provisions of this Decision;

Noting that, in the light of the foregoing, exceptional circumstances exist justifying waivers from the obligations set out in paragraphs (f) and (h) of Article 31 of the TRIPS Agreement with respect to pharmaceutical products;

Decides as follows:

1. For the purposes of this Decision:

   (a) "pharmaceutical product" means any patented product, or product manufactured through a patented process, of the pharmaceutical sector needed to address the public health problems as recognized in paragraph 1 of the Declaration. It is understood that active ingredients necessary for its manufacture and diagnostic kits needed for its use would be included; (1)

   (b) "eligible importing Member" means any least-developed country Member, and any other Member that has made a notification (2) to the Council for TRIPS of its intention to use the system as an importer, it being understood that a Member may notify at any time that it will use the system in whole or in a limited way, for example only in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. It is noted that some Members will not use the system set out in this Decision as importing Members (3) and that some other Members have stated that, if they use the system, it would be in no more than situations of national emergency or other circumstances of extreme urgency;

   (c) "exporting Member" means a Member using the system set out in this Decision to produce pharmaceutical products for, and export them to, an eligible importing Member.

2. The obligations of an exporting Member under Article 31(f) of the TRIPS Agreement shall be waived with respect to the grant by it of a compulsory license to the extent necessary for the purposes of production of a pharmaceutical product(s) and its export to an eligible importing Member(s) in accordance with the terms set out below in this paragraph:

(a) the eligible importing Member(s) (4) has made a notification (2) to the Council for TRIPS, that:

(i) specifies the names and expected quantities of the product(s) needed (5);
(ii) confirms that the eligible importing Member in question, other than a least developed country Member, has established that it has insufficient or no manufacturing capacities in the pharmaceutical sector for the product(s) in question in one of the ways set out in the Annex to this Decision; and
(iii) confirms that, where a pharmaceutical product is patented in its territory, it has granted or intends to grant a compulsory license in accordance with Article 31 of the TRIPS Agreement and the provisions of this Decision (6);

(b) the compulsory license issued by the exporting Member under this Decision shall contain the following conditions:

(i) only the amount necessary to meet the needs of the eligible importing Member(s) may be manufactured under the license and the entirety of this production shall be exported to the Member(s) which has notified its needs to the Council for TRIPS;
(ii) products produced under the license shall be clearly identified as being produced under the system set out in this Decision through specific labeling or marking. Suppliers should distinguish such products through special packaging and/or special coloring/shaping of the products themselves, provided that such distinction is feasible and does not have a significant impact on price; and
(iii) before shipment begins, the licensee shall post on a website (7) the following information:
- the quantities being supplied to each destination as referred to in indent (i) above; and
- the distinguishing features of the product(s) referred to in indent (ii) above;

(c) the exporting Member shall notify (8) the Council for TRIPS of the grant of the license, including the conditions attached to it (9). The information provided shall include the name and address of the licensee, the product(s) for which the license has been granted, the quantity(ies) for which it has been granted, the country(ies) to which the product(s) is (are) to be supplied and the duration of the license. The notification shall also indicate the address of the website referred to in subparagraph (b)(iii) above.

3. Where a compulsory license is granted by an exporting Member under the system set out in this Decision, adequate remuneration pursuant to Article 31(h) of the TRIPS Agreement shall be paid in that Member taking into account the economic value to the importing Member of the use that has been authorized in the exporting Member. Where a compulsory license is granted for the same products in the eligible importing Member, the obligation of that Member under Article 31(h) shall be waived in respect of those products for which remuneration in accordance with the first sentence of this paragraph is paid in the exporting Member.

4. In order to ensure that the products imported under the system set out in this Decision are used for the public health purposes underlying their importation, eligible importing Members shall take reasonable measures within their means, proportionate to their administrative capacities and to the risk of trade diversion to prevent re-exportation of the products that have actually been imported into their territories under the system. In the event that an eligible importing Member that is a developing country Member or a least-

developed country Member experiences difficulty in implementing this provision, developed country Members shall provide, on request and on mutually agreed terms and conditions, technical and financial cooperation in order to facilitate its implementation.

5. Members shall ensure the availability of effective legal means to prevent the importation into, and sale in, their territories of products produced under the system set out in this Decision and diverted to their markets inconsistently with its provisions, using the means already required to be available under the TRIPS Agreement. If any Member considers that such measures are proving insufficient for this purpose, the matter may be reviewed in the Council for TRIPS at the request of that Member.

6. With a view to harnessing economies of scale for the purposes of enhancing purchasing power for, and facilitating the local production of, pharmaceutical products:

> (i) where a developing or least-developed country WTO Member is a party to a regional trade agreement within the meaning of Article XXIV of the GATT 1994 and the Decision of 28 November 1979 on Differential and More Favorable Treatment Reciprocity and Fuller Participation of Developing Countries (L/4903), at least half of the current membership of which is made up of countries presently on the United Nations list of least developed countries, the obligation of that Member under Article 31(f) of the TRIPS Agreement shall be waived to the extent necessary to enable a pharmaceutical product produced or imported under a compulsory license in that Member to be exported to the markets of those other developing or least developed country parties to the regional trade agreement that share the health problem in question. It is understood that this will not prejudice the territorial nature of the patent rights in question;
>
> (ii) it is recognized that the development of systems providing for the grant of regional patents to be applicable in the above Members should be promoted. To this end, developed country Members undertake to provide technical cooperation in accordance with Article 67 of the TRIPS Agreement, including in conjunction with other relevant intergovernmental organizations.

7. Members recognize the desirability of promoting the transfer of technology and capacity building in the pharmaceutical sector in order to overcome the problem identified in paragraph 6 of the Declaration. To this end, eligible importing Members and exporting Members are encouraged to use the system set out in this Decision in a way which would promote this objective. Members undertake to cooperate in paying special attention to the transfer of technology and capacity building in the pharmaceutical sector in the work to be undertaken pursuant to Article 66.2 of the TRIPS Agreement, paragraph 7 of the Declaration and any other relevant work of the Council for TRIPS.

8. The Council for TRIPS shall review annually the functioning of the system set out in this Decision with a view to ensuring its effective operation and shall annually report on its operation to the General Council. This review shall be deemed to fulfill the review requirements of Article IX:4 of the WTO Agreement.

9. This Decision is without prejudice to the rights, obligations and flexibilities that Members have under the provisions of the TRIPS Agreement other than paragraphs (f) and (h) of Article 31, including those reaffirmed by the Declaration, and to their interpretation. It is also without prejudice to the extent to which pharmaceutical products produced under a compulsory license can be exported under the present provisions of Article 31(f) of the TRIPS Agreement.

10. Members shall not challenge any measures taken in conformity with the provisions of the waivers contained in this Decision under subparagraphs 1(b) and 1(c) of Article XXIII of GATT 1994.

11. This Decision, including the waivers granted in it, shall terminate for each Member on the date on which an amendment to the TRIPS Agreement replacing its provisions takes

effect for that Member. The TRIPS Council shall initiate by the end of 2003 work on the preparation of such an amendment with a view to its adoption within six months, on the understanding that the amendment will be based, where appropriate, on this Decision and on the further understanding that it will not be part of the negotiations referred to in paragraph 45 of the Doha Ministerial Declaration.

ANNEX

Assessment of Manufacturing Capacities in the Pharmaceutical Sector

Least-developed country Members are deemed to have insufficient or no manufacturing capacities in the pharmaceutical sector.

For other eligible importing Members insufficient or no manufacturing capacities for the product(s) in question may be established in either of the following ways:

(i) the Member in question has established that it has no manufacturing capacity in the pharmaceutical sector;

OR

(ii) where the Member has some manufacturing capacity in this sector, it has examined this capacity and found that, excluding any capacity owned or controlled by the patent owner, it is currently insufficient for the purposes of meeting its needs. When it is established that such capacity has become sufficient to meet the Member's needs, the system shall no longer apply.