

Annex 9:

Special focus studies

9.1 The WHO/United Nations Prequalification Project

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Annex 9.1:

The WHO/United Nations Prequalification Project

**Good practice documentation
on the contribution of the World Health Organization
and its role in the WHO/United Nations Prequalification Project**

as part of the "3 by 5" Evaluation

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This study and associated documents were developed in partnership with WHO and the “3 by 5” Evaluation Team.

The findings, interpretations, and conclusions expressed here are those of the author and do not necessarily reflect the views of the Evaluation Team.

The Evaluation Team cannot guarantee the accuracy of the data included in this work. International non-proprietary names (INN) (generic names), which are mentioned, do not imply that there are no patents or similar protections to respect.

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List of acronyms

AIDS	Acquired Immunodeficiency Syndrome
AMDS	AIDS Medicines and Diagnostics Service
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
CDC	Centers for Disease Control
CRO	Contract research organization
DIL	Diagnostic Imaging and Laboratory Technology Unit
DRA	Drug regulatory authority
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	Fixed-dose combination
GFATM	Global Fund to fight AIDS, TB and Malaria
GMP	Good manufacturing practices
GPO	Government pharmaceutical organization
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
(L)DC	Least-developed country/Developing country
MOH	Ministry of health
MSF	<i>Médecins sans Frontières</i> (Doctors without Borders)
NACP	National AIDS Control Programme Tanzania
NDRA	National drug regulatory authority
NGO	Nongovernmental organization
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PEPFAR	The President's Emergency Plan for AIDS Relief
PI	Protease inhibitor
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PMTCT	Prevention of mother-to-child transmission
TFDA	Tanzania Food and Drugs Authority
QC	Quality control
WB	World Bank
WHO	World Health Organization
WHOPAR	WHO Public Assessment Report
WHOPIR	WHO Public Inspection Report

1. Introduction

1.1 Objectives

Estimates suggest that currently more than 6 million of the more than 40 million people living with HIV/AIDS¹ are in need of antiretroviral therapy (ART). End of 2003, WHO and UNAIDS jointly launched the so-called “3 by 5” Initiative to accelerate access to treatment and to improve prevention. This initiative aimed at scaling up access to ART for at least 3 million people in need of antiretroviral drugs (ARVs) by the end of 2005.

The availability of an effective and reliable supply of medicines as well as of diagnostics is crucial to the success and expansion of access to treatment. The prequalification of manufacturers and products that act against HIV/AIDS, (and tuberculosis and malaria) is one of the tools to contribute to this goal. WHO’s HIV/AIDS Department has worked closely with the Health Technology and Pharmaceuticals (HTP) Cluster, the Department of Essential Health Technologies (EHT) as well as the Programmes of Medicines Policy and Standards (PSM) and Quality Assurance and Safety: Medicines (QSM).

US\$ 2,828,000 was made available to the cluster from funds received by the HIV/AIDS Department for supporting HIV/AIDS issues.

The Evaluation Team views this part of WHO’s work as a critical cornerstone of the overall strategy of increasing access to treatment. This view is also supported by the members of the Strategic and Technical Advisory Committee for HIV /AIDS (STAC) and strongly expressed in the Reports of its first (December 2004) and second Meeting (April 2005).

1.2 Methodology and sources of information

The format of a “good practice” documentation is being used to:

- document WHO’s involvement to date; and
- identify additional resources needed inside (and outside WHO) to make this cornerstone even more effective for the benefit of the respective countries.

This documentation assesses WHO’s role in the Prequalification Project, documents its contribution, views this project’s overall progress, evaluates its challenges and the future perspectives and makes recommendations for WHO’s continuation in it as part of WHO’s overall contribution to “universal access to treatment and prevention of HIV/AIDS”.

The documentation will be considered as an additional input for the “3 by 5” Evaluation Team. This documentation will not evaluate the Prequalification Project itself but will give the necessary information to help the “3 by 5” Evaluation Team make its conclusions and recommendations on WHO's role in the project.

The documentation takes cognizance of the fact that the Prequalification Project is only part of WHO's actions to support access to AIDS medicines, and that the outcome of this study will also

¹ UNAIDS /WHO AIDS Epidemic Update 2005 report.

be considered in the broader evaluation by the team of the overall impact of the AIDS Medicines and Diagnostics Service (AMDS) on the implementation of “3 by 5”.

The outcome of this documentation will lead to:

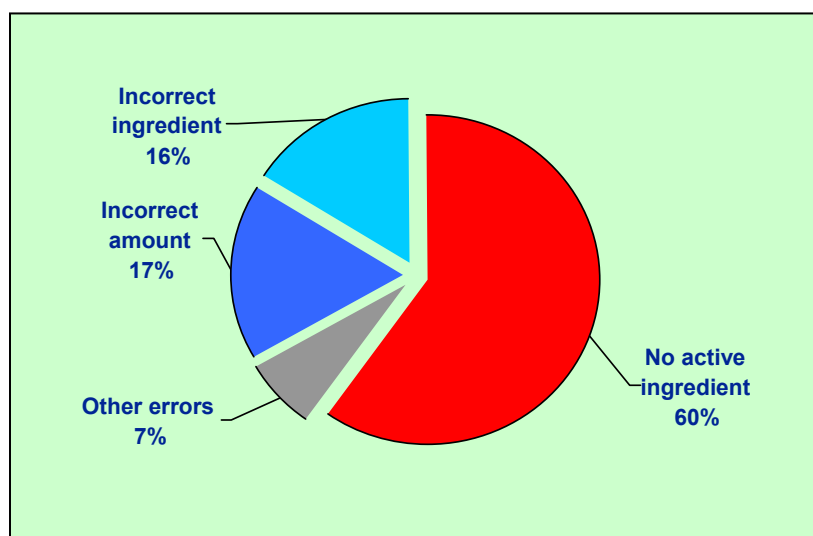
- a clear understanding of WHO’s role in the project;
- an appreciation of WHO’s technical, managerial and coordination role;
- an assessment of partners and stakeholders in the project;
- an assessment of resources needed by WHO to continue playing a major/leading role in the project;
- an assessment of WHO’s strategies to build capacities at regional and country levels;
- a demonstration of the HIV/AIDS department’s ability to collaborate with other clusters/departments of the Organization as part of the evaluation’s organizational analysis.

2. The Prequalification Project

2.1 Background and focus

In 2001, WHO was contacted by drug authorities from developing countries. Help was needed to assure the quality of generic² antiretrovirals (ARVs), which had become increasingly available in the world's poorer regions.

Fig. 1 Breakdown (%) on 325 cases of substandard drugs*



Source: Slide of a presentation by Dr Rágo/WHO

*Antibiotics, antimalarials, antituberculosis, ARVs included. Reported from around the world to WHO database

Why was there a need for quality assurance on ARVs in particular?

Between 2000 and 2002 there was a paradigm shift. Until 2000, treatment was not an option for infected people in developing countries but the situation has changed significantly since then. This is evident looking at the WHO Model List of Essential Drugs. Whereas the 11th edition (December 1999) only mentioned nevirapine and zidovudine (for PMTCT), the 12th edition (April 2002) listed for the first time a wide spectrum of ARVs for HIV/AIDS treatment. The list particularly recommended the use of fixed-dose combinations (FDCs) according to the guidelines issued for *Scaling up antiretroviral therapy in resource-limited settings*.³

In the year 2001, some generic manufacturers – such as CIPLA in India and the Government Pharmaceutical Organization in Thailand – developed the first FDCs consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). The main advantage was that treatment could be simplified as only two tablets had to be taken daily. Such a combination was until then – due to different manufacturers

² There is no generally accepted definition of the term “generic”. In this study “generic” means that there are several manufacturers of equivalent pharmaceutical products. Very often they are called “multisource pharmaceutical products”.

³ WHO, April 2002, revised 2003: www.who.int/hiv/pub/prev_care/en/ARVGuidelinesRevised2003.pdf.

producing the individual brands – not available in countries with stringent national drug regulatory authorities (NDRA).

Nevertheless, it was completely legal to manufacture these drugs in India since the patent law in that country did not protect the *product* as such but rather the *process* by which the product was synthesized. With a change of the route of synthesis, it became legal to “copy” the original.

WHO encountered novel challenges:

- Considering the link in the Model List to the guidelines for scaling up therapy it became obvious that WHO was promoting FDC ARVs.
- FDCs were only available from multi-source manufacturers and cost only a fraction of the originals.
- None of the generic ARV formulations had been registered in countries with stringent drug regulatory authorities (DRAs).
- No generic ARVs could become registered because all APIs were still under patent in all countries with stringent DRAs.
- Because all ARVs are relatively new, the monographs required for the quality controls were missing⁴.
- FDC formulations had already been used successfully in ART projects of NGOs such as *Médecins sans Frontières* (MSF) and there was advocacy pressure on WHO to endorse these treatments.

WHO faced a dilemma. For financial and compliance reasons, the Organization was obviously promoting the use of multisource-drugs, for which there were no guarantees of safety, efficacy and quality.

The available tools for quality assurance systems of supply organizations inside and outside the United Nations were developed to secure the technical quality of long-term approved generic medicines, but no procurement agency had the competence to assess the safety and efficacy on modern agents like ARVs.

Monographs on ARVs were developed for the International Pharmacopoeia⁵ and the idea of the Prequalification Project was conceived by the WHO department Medicines Policy and Standards (HTP/EDM), more precisely by the technical unit Quality and Safety of Medicine (QSM).

Following a thorough discussion within the Expert Committee and a briefing with the ICDRA (International Conference of Drug Regulatory Authorities), guidelines were drafted. From the outset, the project’s political dimension was clear to the department. Therefore, considerable time was spent on the groundwork. The preliminary work was comprehensive, in that the technical process tried to mimic normal registration procedures (from stringent authorities). On the other hand, care was taken that the project was fully approved by the official channels inside WHO.

Outside WHO, the United States Food and Drug Administration and French, Nordic and African authorities had been briefed on the project before its start.

⁴ Monographs are well-established and approved laboratory procedures to control the quality of, e.g. active pharmaceutical ingredients, excipients and dosage forms. These monographs are listed in pharmacopoeias, which are widely available. Well-recognized pharmacopoeias are, e.g. the British Pharmacopoeia (BP), the United States Pharmacopoeia (USP), the European Pharmacopoeia, and the International Pharmacopoeia (IP) issued by WHO.

⁵ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/mon_arvs/en/index.html.

Eventually, the Prequalification Project was not launched by WHO but by the United Nations in 2001, with the objective of providing quality assessment on a selected number of pharmaceutical products being considered for purchase by United Nations agencies.

The project is backed by WHO, UNICEF, UNFPA and UNAIDS, with additional support from the World Bank. WHO was chosen to manage the project and UNICEF to provide administrative support and infrastructure.

In general, the medicines for high-priority diseases (HIV/AIDS, malaria and TB) and quality control laboratories are eligible to undergo the prequalification procedure.

In March 2002, WHO issued its 1st edition of the Prequalification List

WHO and pharmaceutical guidelines

The WHO has a long history and an excellent reputation within the pharmaceutical world. It was the first organization to issue guidelines⁶ on good manufacturing practices (GMP⁷) for pharmaceutical products in 1967, which were prepared by a group of WHO consultants at the request of the 20th World Health Assembly (resolution WHA20.34).

WHO developed the concept of pharmaceutical efficacy, safety and quality. To this day, WHO plays a leading role in developing and updating guidelines for the pharmaceutical sector. Virtually all GMP guidelines of all national DRA are based on the WHO GMP guidelines. In particular, PIC/S and EU-GMP guidelines are harmonized with WHO GMP. The PSM department possesses an extremely high level of pharmaceutical technical knowledge.

With vast in-house knowledge and the worldwide authority of WHO this was an ideal foundation on which to launch a scheme to qualify pharmaceutical products so as to assist countries where a stringent NDRA did not yet exist.

Meanwhile, there are several pre-qualified medicines to treat HIV/AIDS and opportunistic infections from both innovators and generic manufacturers, and there are three approved quality control laboratories. Up-to-date lists are provided by WHO under <http://mednet3.who.int/prequal/>.

Other funding institutions and donor agencies such as the Global Fund to fight AIDS, TB and Malaria (GFATM) and the World Bank (WB) accept the standards set by WHO, which are integrated in their procurement guidelines.

⁶ WHO GMP guidelines: http://whqlibdoc.who.int/publications/2004/9241546190_part1.pdf.

⁷ WHO GMP definition: Good manufacturing practice is that part of quality assurance that ensures that products are consistently produced and controlled in regard to the quality standards appropriate to their intended use and as required by the marketing authorization.

Focus

The Prequalification Project, which once started as a pilot project, has now gained a significant momentum of speed, influence and attention. Several WHO clusters and departments are involved. There are also links, cooperation and coordination at local, regional and global levels.

The prequalification of a product and of the relevant manufacturer consists basically of two parts: first, the Good Manufacturing Practices (GMP) standard of the manufacturing process and site and second, the assessment of the dossier. The dossier includes all necessary quality specifications, data on the safety and efficacy of the products and product information and labelling. Safety and efficacy data include, but are not limited to, a bioequivalence study in humans.

On the one hand, the Prequalification Project could be regarded as a scientific and technical assessment of HIV/AIDS medicines quality, safety and efficacy. It uses the same scientific principles and standards as any well-established regulatory agency for medicines does.

On the other hand, since all ARVs are still under patent in all industrialized countries and in many developing countries, the quality approval through a United Nations agency is of highest political, economic and public-health interest.

2.2 Prequalification of medicines, CROs, API manufacturers and laboratories

The entire Prequalification Project has been designed according to stringent international registration standards. The product's quality is assured through an audit of the manufacturing site according to WHO good practices and a set of other guidelines⁸. The safety and efficacy is assured through registration guidelines⁹. Special care has been taken for FDCs, when there is no originator fixed-dose combination available¹⁰.

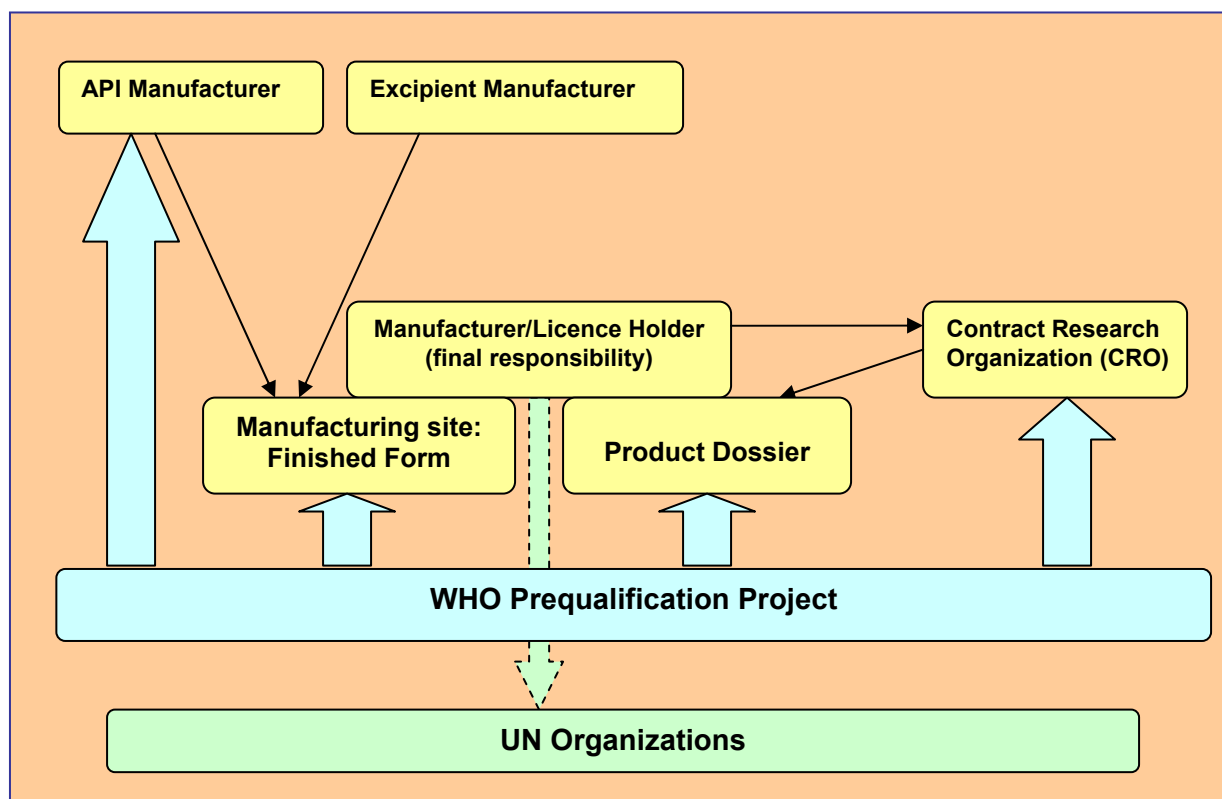
Figure 2 shows that the WHO prequalification checks all quality-, safety- and efficacy-related issues before a product is approved for purchase by United Nations organizations. **The final responsibility for the products lies with the manufacturer.** This system is not different from DRAs like the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA).

⁸ http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf.

⁹ Multisource (generic) products have to meet the requirements as described in *Marketing Authorization of Pharmaceutical Products with special Reference to Multisource (Generic) Products: a Manual for a Drug Regulatory Authority*, WHO/DMP/RGS/98.5 and Annex 9, WHO Technical Report Series No 863.

¹⁰ *Guidelines for registration of fixed-dose combination medicinal products*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No.929).

Fig. 2 WHO prequalification process



At first, the prequalification focus rested only on the finished form and its producer. However, this was broadened as the project developed, so that now API manufacturer and CRO must be checked and pre-qualified as well. However, since contract research organizations (CROs) and active pharmaceutical ingredient (API) manufacturers were not audited at the beginning of the project, there is a backlog of missing audits or audit reports published by WHO.

For European DRA, the practice is that the manufacturing site is always inspected, while the API¹¹ manufacturer and the CRO are hardly ever inspected. The EMEA itself does not conduct site inspections. EMEA relies on audits that have been conducted by one of their member countries. There is a trend toward EMEA DRA handling API audits in a stricter manner.

Currently,¹² 68 finished forms of ARV and 35 drugs against opportunistic infections are prequalified. **Out of the 68 ARVs, 34 are multisource products and 34 are brand products.**

Prequalification of laboratories

The quality control (QC) of labs has a different approach. The idea behind this is that there should be independent regional reference laboratories for the purpose of quality monitoring of medicines against HIV/AIDS, malaria and TB drugs.

¹² WHO prequalification list 26th edition dated 29 September 2005.

Currently, three prequalified laboratories exist. Since they were just recently prequalified and are located in countries with relatively advanced NDRAs, it is not yet clear how these laboratories can enhance the quality or the access to HIV/AIDS, malaria and TB drugs. It will be interesting to see the activities of the first laboratories in least-developed country (LDC) high-prevalence countries.

Table 1
Prequalified laboratories

Edition	Date	Change
1 st edition	22.06.2005	Added Centre for Quality Assurance of Medicines (CENQAM) P/Bag X 6001 Northwest University Potchefstroom, 2520 South Africa
2nd edition	05.07.2005	Added Research Institute for Industrial Pharmacy (RIIP) P/Bag X 6001 Northwest University Potchefstroom, 2520 South Africa
3rd edition	27.10.2005	Added <i>Laboratoire National de Contrôle des Produits Pharmaceutiques</i> , LNCPP <i>Direction Générale Polyclinique Ahmed Aroua</i> , Rond point Sidi Yahia, 16035, Alger, Algérie

2.3 Transparency of the project

In the first year, the Prequalification Project was started as a pilot project because the management was not sure whether the project would survive. The project purposely started with a low profile so as not to attract too much attention.

However, the project was heavily criticized by the United States' Hudson Institute. The United States delegation claimed that in addition to other points the project was "not transparent". In the World Health Assembly Resolution (WHA57.14) on 22 May 2004, the Prequalification Project was backed and the Director-General called on WHO "*to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available*".

As a result, WHO devised the so-called:

- WHO Public Inspection Reports (WHOPIR) and;
- WHO Public Assessment Reports (WHOPAR).

The **WHOPIR** is a summary of the findings during the inspection, and exclude confidential proprietary information:

- for a manufacturing site of **finished products** (FPs);
- for a manufacturing site of **active pharmaceutical ingredients** (APIs);
- for an organization such as a **contract research organization** where a bioequivalence study or other clinical study have been performed (CROs);
- for **quality control laboratories** (QCLs).

The **WHOPAR** is the summary of the assessment of the products dossier. The WHO Prequalification Project is widely transparent. WHOPIR and WHOPAR are written with the consensus of WHO and the concerned manufacturer/organization. Only those reports are published where the products were assessed successfully. Negative results are not published. WHO argues that otherwise manufacturers would not take part in the project and that negative

results could interfere with current national GMP findings. However, the list is not up to date. There are reports missing for products listed months ago.

Neither the United States FDA nor EMEA offers the transparency of the WHO Prequalification Project. Furthermore, easy-to-understand instructions are provided on the homepage¹³ of the Prequalification Project with links to further guidelines and/or examples and checklists.

2.4 Involvement of WHO: WHO's technical, managerial and coordinating role

The Prequalification Project has been developed within WHO with the participation of several departments. The Department of Health Technology and Pharmaceuticals (PSM) and in particular Quality and Safety of Medicines (QSM) had all the necessary technical knowledge to translate an idea into a project. Because of the potential political and technical implications of the project, WHO looked for support from other United Nations organizations, especially UNICEF. UNICEF's involvement is limited to offering conference rooms where the assessors regularly meet. UNICEF will be involved more in the future as WHO and UNICEF agreed to share the salary of a coordinator in Copenhagen to organize the assessor's meetings.

The PSM Department is taking the lead for the technical, managerial and coordinating role. The team in charge of the project consists of only **three scientific staff**.

2.5 Achievements of WHO's Prequalification Project

The main achievements of the Prequalification Project are:

- a) setting a quality benchmark;
- b) embedding confidence in generic products;
- c) price reduction through (generic) competition and thus enhancing affordability and availability;
- d) linkage with procurement and funding organizations; and
- e) building up local capacity.

a) Setting a quality benchmark

ARVs are expensive pharmaceuticals – even as generics. Compared to other chronic diseases such as TB, the HIV/AIDS treatment costs several times more! This and the growing demand for ARVs have produced an increasing number of manufacturers offering these drugs. Even for an experienced procurement organization, it is almost impossible to judge the quality of the resulting products. The quality approach of the Prequalification Project is so high that a successful product application represents a high product quality.

b) Embedding confidence in generic products

Typically there is an endless battle between the originators and the generic manufacturers on the quality issue of the generic products. Quality plays an important role, particularly in the field of HIV/AIDS treatment. Substandard or faulty products are likely to endanger the treatment progress because of decreased efficacy. This can trigger resistance development,

¹³ Web site homepage of the Prequalification Project: <http://mednet3.who.int/prequal/default.htm>.

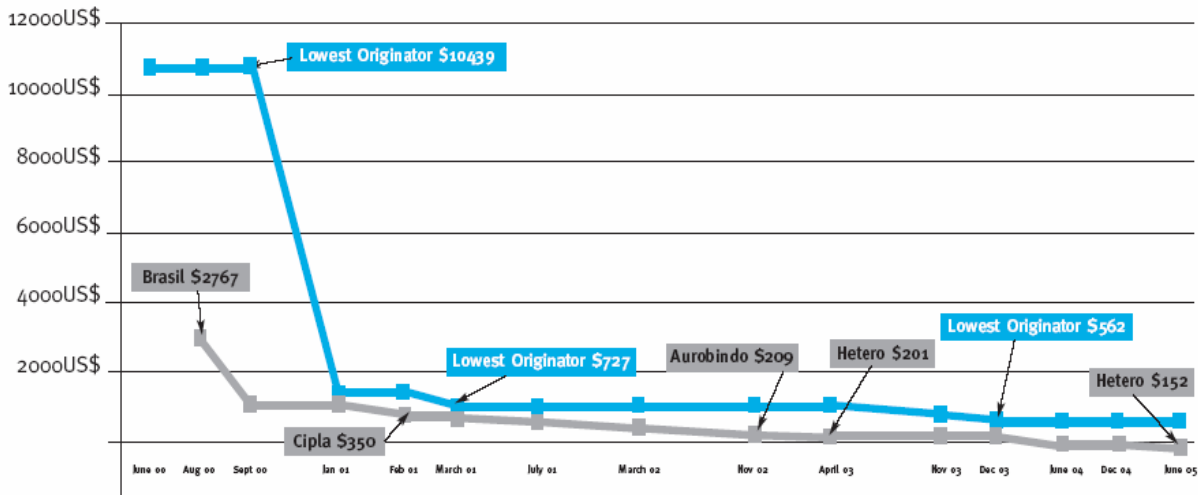
which leads to illness and finally to death. Concerns about quality of ARVs have to be treated seriously.

Due to the high technical quality of the prequalification approach, the extensive discussions among expert groups before the project’s launch and the worldwide acceptance and authority of WHO, the prequalification could embed confidence in generic products. It was appropriate to invite originators as well as generic manufacturer. Although originators still have some reservations, the majority accepts the role of WHO as a competent guide on quality.

c) Price reduction through (generic) competition, enhancing affordability and availability

Figure 3 shows that generic competition leads to lower prices. Although the price reduction started before the beginning of the prequalification process, the WHO project documented that low prices do not automatically mean lower quality. The treatment roll-out is directly linked with the lower prices of ARVs.

Fig. 3 Effect of generic competition on lowering drug prices
May 2000-June 2005



Sample of ARV triple-combination: stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). Lowest world prices per patient per year. Generic competition has shown to be the most effective means of lowering drug prices. During the last four years, originator companies have often responded to generic competition.

Source: Médecins sans Frontières. *Untangling the Web of Price Reductions*, • June 2005 •, 8th ed.

d) Linkage with procurement and donor organizations

Right from the start of the Prequalification Project, WHO was looking for partners that could have practical benefits from the project’s outcome. To date, there are no generally accepted international standards on quality assurance for procurement organizations. Although all the well-known international procurement agencies do have their own quality assurance system, none is as extensive as the WHO project. Existing guidelines of procurement agencies concentrate on GMP issues but do not cover the efficacy and safety of drugs.

Therefore, WHO’s idea was that the Prequalification Project could assist these organizations. A strong link was established to UNICEF in that the dossiers are checked at UNICEF premises and with UNICEF organizational assistance. Meanwhile, practically all procurement

organizations, e.g. the Interagency Procurement Services Office (IAPSO) or IDA ARV Procurement Services appreciate the prequalification and consider it obligatory (partly depending on the donor). Since the Global Fund acknowledged the WHO prequalification as an accepted quality standard at the same level as, e.g. the United States FDA or PIC/S, the reputation of (and attraction to) the WHO project was strengthened.

e) **Building up local capacity**

There are some positive “side effects” of the project, mainly for:

- **The audited or applying (generic) manufacturer**
 - By taking part in the prequalification process the generic manufacturer learns much about international norms and standards. It is a well-known fact that a dossier assessment and site audit is almost as good as a consultancy. Furthermore, WHO gives advice, e.g. on expected clinical data and other relevant issues to help inexperienced manufacturers.
- **Auditors and assessors**
 - WHO takes care that when audits are conducted the NDRA of the manufacturer is always present. NDRA auditors with less experience gain much from experienced colleagues of stringent drug authorities.
 - The same holds true for the team of assessors: the group includes representatives of various authorities but assessors from developing countries are always included in the team.
- **National drug regulatory authorities (NDRAs)**
 - For NDRA in developing countries, a lesson they had to learn is that an authority can demand data such as the bioequivalence study. For example, due to the WHO prequalification in the United Republic of Tanzania, bioequivalence data are now one of the requirements for ARVs to obtain national registration.

2.6 Capacity of the Prequalification Project: resource needs for WHO to continue playing a leading role in the project

Staff-wise, the prequalification team consists of very few people and the budget is small. The biennium budget for 2004–2005 was US\$ 4.7 million, with only 3.6 staff members in the unit: three professionals and one shared secretary. The coordinator of QSM, Dr Lembit Rāgo, does not count as a staff member of the prequalification team. In the future, there will be a shared secretary with UNICEF for the assessors meetings to take place in Copenhagen.

The audits and dossier assessments are conducted by a team of external experts. They are normally recruited as “volunteers” from drug regulatory authorities so that only travel allowances need to be paid.

The Clinton Business Plan¹⁴ makes a clear analysis and gives future recommendations. The budget needed is estimated at US\$ 12 million for 2006–2007. The WHO approved budget is US\$ 8.9 million for the next biennium. Compared to 2004–2005 this is a significant increase of the total budget. But it must be noted that the contribution from the regular WHO budget in 2006–2007 will be even smaller than in 2004–2005. The increase in budget means only that the Prequalification Project is “allowed” to raise funds to fill the gap.

¹⁴ In September 2005 a business plan was developed in partnership between WHO and the Clinton Foundation HIV/AIDS Initiative to run the project effectively and efficiently and to determine the funds needed.

Due to the fact that only about 30% of all WHO funds are secured through the regular budget, the “normal” procedure of WHO with regard to approved department needs is to allow the department to raise extra-budgetary funds.

An important comment from AMDS was made in this regard:

“Key strategic operations should not be vulnerable because of donor pressure”

Furthermore, fundraising is time-consuming. The prequalification team has no extra time to do this. The department’s output is impressive and significant. The unit consists of highly competent, committed and hard-working staff. Despite all their efforts, however, there is a backlog of dossiers, inspections, web reports, etc. which, if not addressed, will eventually endanger the quality and reputation of the project. Moreover, there is the danger that experienced and highly qualified staff may leave the project due to work overload (one experienced auditor left already in 2005).

The Prequalification Project is widely regarded as an important cornerstone for scaling up ART. It is, therefore, necessary for WHO to safeguard and strengthen its existence and future contribution.

3. Prequalification of diagnostics

In 1985, the first HIV diagnostics were introduced but did not perform very well; the WHO Global Programme on AIDS decided to provide guidance on quality. In 1988, WHO assessment of HIV diagnostics began. Since then, different tests have been validated and the manufacturers inspected by the Diagnostic Imaging and Laboratory Technology unit (DIL) which falls within the Essential Health Technologies (EHT) Department in the Medicines and Technology for Health (HTP) Cluster. A regular report is issued in collaboration with UNAIDS.

This report is far more than a list of prequalified tests. It describes the:

- diagnosis of HIV infection;
- HIV testing strategies;
- Follow-up after diagnosis;
- laboratory safety;
- assay selection; and
- materials and methods of assessment.

Eventually, the various tests are listed in a table including technical data and price information. These reports are the standard reference for diagnostics and strategies in many ART projects. Almost all tasks (except test validation) are carried out within DIL by a team of two experts.

Diagnostics do not usually attract the same attention as medicines. Too many different techniques exist and complicated procedures as well as varying lab performances are irritating. Clear guidance, particularly in the HIV/AIDS field, as provided by WHO/DIL is therefore of utmost importance.

The diagnosis – particularly in children below 18 months – and the ongoing monitoring (CD4, viral load, resistance patterns) are some of the major challenges in scaling up and maintaining treatment projects.

If organizations and governments involved do not want to be driven by manufacturers and their promotion machinery, a strong pro-active diagnostic department is needed. WHO should ensure the necessary funding so that DIL can conduct and extend all necessary services to assess HIV/AIDS diagnostics.

Ideally, DIL and AMDS should cooperate to identify diagnostic trends and assess promising effective and efficient techniques.

4. Cooperation between the Prequalification Project and the HIV/AIDS Department

As the organigram in Annex C shows, the prequalification of medicines is placed within a technical unit under the Health Technology and Pharmaceuticals (HTP) Cluster/Department of Medicines Policy and Standards (PSM).

Inside the Department on HIV/AIDS, the **AMDS¹⁵** is “a mechanism created to expand access to quality, effective treatment for HIV/AIDS by facilitating the increased supply of ARVs and diagnostics in developing countries”. The AMDS is the access and supply arm of UNAIDS/WHO “3 by 5” Initiative. There should not be the misunderstanding that AMDS is a procurement agency. AMDS is a **technical assistance for governments and relevant treatment providers**.

In fact AMDS is “hosted” at WHO headquarters but does not fit into “normal” structures. To fulfil its mission, AMDS has a vital interest to link and to support prequalification of medicines and diagnostics.

The prequalification from the view of AMDS has major strategic health implications. Because generic ART are not longer “second-choice”, rapid scale-up was/is possible. For AMDS, the Prequalification Project is extremely important for the future of treatment access.

Since the Prequalification Project is so important for AMDS, it helped shift funds from the HIV/AIDS department to the Prequalification Project during times when finances were lacking. Furthermore, the HIV Department helps raise funds for the prequalification unit.

Although there are common goals between AMDS and the Prequalification Project on medicines, there are no regular meetings and exchange of information. It seems the communication between the departments and units is irregular and ad hoc. AMDS expressed the need for regular meetings and updates. Meetings should cover the following topics: new product entries, current products in the prequalification process pipeline, obstacles for certain products, forecasting/new treatment developments, and current developments of important issues such as FDA tentative approvals.

¹⁵ <http://www.who.int/3by5/publications/briefs/en/amds.pdf>.

5. Direct or indirect influence of the Prequalification Project on increased access to ART

5.1 Comments from various sources

Médecins sans Frontières: "...the project has dramatically improved access to affordable quality medicines, particularly AIDS drugs."

World Bank: "...one of the most useful, if not the most useful, practical tool provided by WHO and the United Nations agencies during the past years".

AIDS Medicines Diagnostics Service: "The scale-up would not have been possible – generics are not longer second choice."

Clinton Foundation: The savings achieved as a result of prequalification are so significant that the return on investment in the Prequalification Programme can be estimated at US\$ 200 saved to US\$ 1 spent on the programme, based on the use of first-line ART in Africa since 2004.

GlaxoSmithKline: "Given the urgency of the HIV crisis, GSK accepts that the WHO Prequalification Scheme has a role to play in helping to inform local regulatory approval and scale-up availability of WHO recommended ARVs. However, the Scheme should never be seen as a formal regulatory assessment process."¹⁶

Hudson Institute: "There are several problems in the prequalification process, not the least being the fact that WHO isn't a regulatory agency and has no enforcement powers."
"...WHO prequalified products [...] are copy drugs rather than generics."

HUDSON INSTITUTE

Major criticism was raised primarily by United States organizations, in particular, the Hudson Institute¹⁷. The Hudson Institute is a conservative non-profit organization based in Washington, D.C. Its views are very much United States- focussed and there are links to various United States firms (Funders listed in the institute's annual report 2002: Ciba-Geigy, Merck & Co, Novartis, Procter & Gamble, etc.). The Hudson Institute criticized in particular the fact that "copy drugs" with unknown safety and efficacy had been prequalified by WHO. The term "copy drug" was used for (fixed-dose) combinations of ARVs, which were not available as brand products and was meant to discredit the quality of those drugs compared to true generic drugs qualified by United States FDA. However, the Hudson Institute's arguments are not valid since the United States FDA itself drafted guidelines (Guidance for Industry Fixed-Dose Combination and Co-Packaged Drug Products for Treatment of HIV) and tentatively approved lamivudine/zidovudine plus nevirapine as co-blister from ASPEN South Africa, a "copy drug" according to Hudson Institute!

¹⁶ GlaxoSmithKline's position on WHO Prequalification Scheme for ARVs - August 2005.

¹⁷ For more information please access www.hudson.org and www.sourcewatch.org/index.php?title=Hudson_Institute.

Generally, the Prequalification Project is seen as one of the cornerstones in increasing access to ART.

5.2 Prequalification and pricing

The prequalification of products costs pharmaceutical manufacturers considerable additional resources. The product and therefore the whole manufacturing process, including the analytical equipment, the manufacturing of APIs and excipients must be determined to be GMP compliant.

To achieve GMP compliance, the manufacturer normally must invest in higher-quality, and thus in more expensive raw materials, equipment and production facilities.

Furthermore, clinical data for the dossier must be assessed and usually a bioequivalence study must be conducted. A bioequivalence study alone can cost between US\$ 40,000 and US\$ 150,000 per product.

Is this investment reflected in the prices offered by generic manufacturers?

To estimate the influence of prequalification on the cost of products, typical WHO first-line ARV products are compared, including FDC prequalified and non-prequalified products.

Table 2
Comparison of prequalified generic products with their non-prequalified competitors

Products prequalified as of April 2005 (23 rd list)							Average price	
Lamivudine 150/ Stavudine 30/ Nevirapine 200	Aurobindo 144	Cipla 175	<i>GPO</i> <i>341*</i>	Hetero 147	Ranbaxy 219	Strides 168	US\$ 170.60	
Lamivudine 150/ Zidovudine 300	Aurobindo 204	Cipla 182	GSK 237	<i>(GPO)</i> <i>426*</i>	Hetero 190	Ranbaxy 197	Strides 204	US\$ 202.33
Nevirapine 200	Aurobindo 112	<i>Boehringer</i> <i>438^a</i>	Cipla 73	<i>GPO</i> <i>255*</i>	Hetero 77	Ranbaxy 84	Strides 80	US\$ 85.20

Source: Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS” (UNICEF – UNAIDS – WHO – MSF, June 2005). Prequalified products are in bold.

^aThe most expensive products (more than double the price of the cheapest products) have not been taken into account to avoid distortion of the analysis.

From Table 2 it can be concluded that prequalified generic products are either cheaper or in the same price range as their non-prequalified competitors. Obviously the disadvantage of having to invest in costly raw-materials, equipment and clinical studies is compensated for by the products’ higher sales volume.

6. Acceptance

6.1 Prequalification and national drug authorities (NDRAs)

When it comes to national drug regulatory authorities, the world is divided into different standards and markets. Unfortunately, although the standards are similar, they are not yet harmonized, so that different NDRAs are not obliged to accept inspections or dossier assessments from other authorities. The most important authorities and markets are listed as follows:

European Union
United States of America
Japan

} **ICH Countries**

PIC/S countries outside the above-mentioned countries or regions are e.g. Malaysia, Romania, Singapore or Switzerland. Due to strict assessment of the DRAs, PIC/S ensures that authorities adhere to GMP inspection guidelines.

Drug regulatory authorities from the International Conference on Harmonization (ICH) and PIC/S countries are often called “stringent”.

For all above-mentioned authorities, the WHO Prequalification Project has no direct impact because the prequalification cannot replace or ease existing registration requirements.

All other countries are seen (from a Northern perspective) as RoW ("rest of the world"). Particularly in developing countries, where the burden of HIV/AIDS is high, the NDRAs are often weak or do not exist.

However, even in this context, there are quite remarkable differences: Whereas NDRAs in Uganda and the United Republic of Tanzania are relatively strict and have gained power, others such as in Angola and the Democratic Republic of Congo are reported to be extremely weak.

In the United Republic of Tanzania, prequalification is seen as an added advantage in the decision-making process for the Tanzania Foods and Drugs Authority (TFDA). However, TFDA believes that prequalification should not “overrule” the national registration. According to TFDA WHO should use the prequalification as a tool to build up (human) capacities in (L)DC. Auditors and assessors in LDC should regularly take part in prequalification issues to strengthen the personnel of local drug authorities.

There are manufacturers, particularly in Asia, that are well known for their quality and are therefore often even used as contract manufacturers for the United States and European markets. If these manufacturers wanted to manufacture and sell ARV products to international donor organizations they could be excluded because international tender guidelines regularly demanded registration in one of the ICH or PIC/S countries. However, such a registration of a generic ARV is impossible because medicines are under patent in each single ICH or PIC/S country. For these high-quality manufacturers, these tender regulations were a clear disadvantage.

Prequalification and EMEA/United States FDA

The European Medicines Agency (EMA) is the decentralized drug regulatory body of the European Union, with headquarters in London. It acts as coordinating authority of the 25 EU Member States in a network. If, e.g. a manufacturer aims for a European registration, the process is coordinated by EMA but executed by two different European DRAs (e.g. the United Kingdom and Germany). One acts as rapporteur and the other as co-rapporteur.

The WHO prequalification does not play a role for the territory of the European Union.

However, there has been a major breakthrough in this regard:

The EMA has, for the first time, adopted scientific opinions on medicinal products intended exclusively for markets outside the European Union¹⁸. A new provision was made under the revised EU pharmaceutical legislation (**Art 58**). This allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to offer opinions, at the request of WHO, on products that are intended for use outside of the EU. Since this article 58 has just been introduced, there is no experience on it (two GSK products are in the pipeline). **Potentially it could have a major impact on reinforcing the Prequalification Project since EMA is now legally entitled to support WHO.**

Thomas Lönngren, EMA Executive Director, stated: "It is very positive that the European Medicines Agency has been able to work with WHO on putting in place this new way of assisting countries outside the EU to allow faster access to important medicines in response to public health challenges."

United States FDA

The United States FDA is an authority with the intention of protecting the United States citizen. It allows the import of drugs only if they are fully registered. When the PEPFAR initiative was launched, the pharmaceuticals that were to be bought had to fulfil the requirements of the United States FDA. As a result, generic ARV drugs – even WHO prequalified drugs – were practically excluded from purchase.

Recently, two significant changes have taken place:

- The FDA is now allowed to issue a so-called "tentative approval". A "tentatively approved" drug fulfils the quality expectations of the United States FDA but cannot be registered and traded in the United States. The first tentative approval was issued to Aspen's lamivudine/zidovudine FDC, as a co-blister along with nevirapine tablets in January 2005.
- Guidelines on FDCs are developed that are similar to WHO guidelines. Consequently, ARV FDCs – which were treated formerly as an entirely new drug, can obtain "tentative approval".

Looking more closely at the **United States FDA tentative approval**, it appears that it is a copy of the **WHO Prequalification Project** (no fees, fast track, FDC, no registration) – but there is no mutual recognition of these two approvals.

The FDA and the WHO prequalification team do, however, exchange information on a regular basis.

¹⁸ <http://www.emea.eu.int/htms/hotpress/d38247705.htm>.

It is impressive how the Prequalification Project has influenced the two most powerful drug regulatory authorities.

While EMEA's intention is to assist WHO, the United States FDA was under pressure – after extreme criticism – to develop its own scheme to allow the use of cheap ARVs in developing countries.

It will be a major challenge to join these efforts but also a unique opportunity. If WHO prequalification and the United States FDA tentative approval would support (and ideally recognize) each other's certification schemes, workload could be reduced and acceptance increased.

6.2 Prequalification and financing agencies

It is difficult to determine exactly how many patients are receiving ART from the donor institutions, but it is very clear which organizations take the lead in financing ART:

These are:

- The Global Fund
- World Bank
- USAID/PEPFAR
- National budgets of the (L)DCs (e.g. Brazil, Thailand).

The Global Fund has an approved budget¹⁹ of **US\$ 3.4 billion** of which 49% was spent on drugs and commodities (for HIV/AIDS TB and malaria). Until 2008, a total of US\$ 6.1 billion has been pledged and/or contributed to the Global Fund. A substantial part of this budget is being spent on the financing of ARV. The Global Fund was the first major non-United Nations agency to adapt the prequalification standard within their procurement guidelines:

These are the three accepted quality standards of the Global Fund:

Option A: is approved by the WHO Prequalification Project

Option B: is approved by a stringent regulatory authority (ICH or PIC/S)

Option C: (i) if there are less than two suppliers that meet the A or B standard, the product can be bought from any source if the manufacturer has submitted the product for approval to WHO or an International Conference on Harmonization (ICH) or PIC/S member *and* the manufacturing site is GMP-compliant.

(ii) if the product cannot be sourced from two or more suppliers according to any of the above-mentioned criteria, it can be sourced from any GMP-compliant manufacturer.

IMPORTANT: Option A and B are considered equal, meaning that no preference is taken by the Global Fund for either option, whereas option C (i) can only be used if options A or B are not applicable. Option C was only introduced because of limited sources and intended only to be an option for a limited time.

¹⁹ The Global Fund: Letter to all pharmaceutical companies, 15 June 2005.

Limitations: Information on products that meet option A is easy to obtain, information on option B is possible whereas information on option C is hard to obtain. Furthermore, option C offers a loophole to manufactures. They can submit a dossier and thus become eligible but can then withdraw from the approval process later on.

Another exemption is the 90-day rule, meaning that if an option A or B supplier cannot deliver within 90 days, option C could be applied.

From the pharmaceutical perspective, the Global Fund clearly compromised in quality. Option C is of *unknown* quality to the Global Fund. However, this could be balanced through a good quality assurance system of the purchasing organization.

The World Bank provides for a significant part of the national (health) budgets in many LDC, either in the form of a loan or a grant.

The Treatment Acceleration Program (TAP) makes US\$59.8 million available to three pilot projects in Burkina Faso, Ghana and Mozambique. TAP builds on the April 2004 partnership agreement that was signed by the GFATM, UNICEF and the Clinton Foundation in order to make high-quality AIDS medicines available at low prices to developing countries.

TAP is the first World Bank-funded project to focus primarily on HIV/AIDS treatment in Africa. The Prequalification Project is “an essential contribution to establishing a solid basis for quality drug supplies within international health programmes²⁰”.

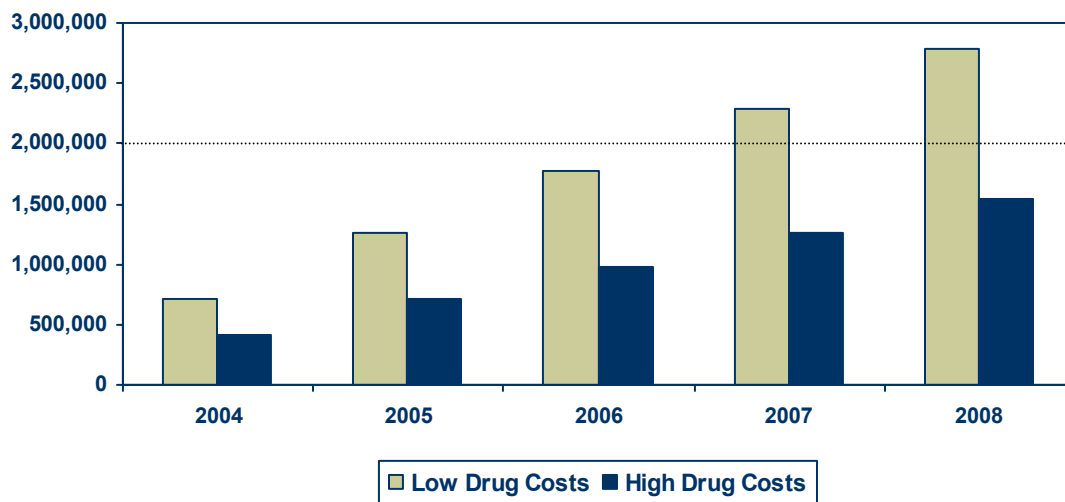
Under **USAID**, the **PEPFAR**²¹ money (**US\$ 15 billion over five years**) is meant to be spent (beyond other projects) on ARVs. The only accepted standard is the United States standard, meaning that **all drugs must be United States-FDA approved**. This has produced strong criticism since it was seen as an American business development rather than aid and it is evident that this major financial resource had relatively little impact. The WHO prequalification is *not* accepted here. No other funding agency has such strict and protective “quality standards”.

Furthermore, the United States FDA standard leads to higher cost because only originator drugs can be purchased and though the prices of brands are reduced for LDCs, eventually the roll out is almost 50% less than when using “low cost drugs” (Fig. 4).

²⁰ Source: World Bank’s statement at the stakeholders meeting on 26 September 2006, WHO headquarters.

²¹ The Emergency Plan aims to support treatment for at least 2 million people living with HIV/AIDS, prevent 7 million new infections, and support care for 10 million people infected with and affected by HIV, including orphans and vulnerable children. The Emergency Plan works in over 120 countries around the world, with a special emphasis on 15 countries in Africa, Asia and the Caribbean. These countries—which are home to approximately 50% of HIV infections worldwide—are Botswana, Côte d’Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, the United Republic of Tanzania, Uganda, Viet Nam and Zambia.

Fig. 4 **Reaching targets within PEPFAR budget – number of ARV patients under low and high drug cost scenarios**



Source: Resource requirements for reaching the treatment goals under PEPFAR, Presentation at XV International AIDS Conference, Owen Smith, Abt Associates Inc., Gilbert Kombe, Abt Associates Inc. Bangkok, 15 July 2004.

National budgets play a part that should not be underestimated. Not only in Brazil, where 100% of the ART treatment is covered by the national budget, and Thailand but also in LDC a part of the budget is usually covered by the regular budget. Since national budgets are not bound to certain donor guidelines there is flexibility for the procurement of domestically produced drugs. In Thailand, for example, prequalification is not required, but GPO – the state-owned manufacturer of ARV – intends to go through the process. In 2006, the Government of the United Republic of Tanzania plans to spend US\$ 18 million on recently developed locally manufactured ARVs that are not WHO prequalified.

7. Problems

7.1 Delistings and withdrawals

A major drawback for the Prequalification Project was the removal and withdrawal of formerly prequalified drugs from the published list.

A number of CIPLA and Ranbaxy drugs were removed in May and August 2004. The reasons given were the same for both companies: inspections at the CRO revealed non-compliance of Good Clinical Research Practice (GCP), Good Laboratory Practice (GLP) and data verification of the bioequivalence study. Although the CRO were subcontractors of CIPLA and Ranbaxy, the final responsibility with the product always lies with the manufacturer. If the contract CRO data are wrong, the licence holder/manufacturer is responsible.

That same year in November, Hetero and Ranbaxy voluntarily withdrew all their drugs after WHO wrote a “warning letter” to all manufacturers to check the contact research organization that conducted bioequivalence studies.

The criticism raised afterwards, even from inside WHO, was mainly:

- WHO reaction was too harsh (delisting of CIPLA and Ranbaxy);
- WHO is not able to ensure quality; and
- WHO communication/guidance is poor.

Was the reaction of the prequalification team really too strict?

From the perspective of a drug regulatory authority (DRA), the answer is very clear: there was no other choice than to withdraw the product. Bioequivalence is such a crucial part that if there is any doubt then there is no choice. If fraud was involved (and it was insinuated that WHO was purposely provided with wrong clinical data), even a ban of the manufacturer could have been considered (which is the usual practice at the United States FDA).

Was the substandard avoidable? Is WHO able to ensure quality?

As mentioned earlier, WHO copied common European audit practices where CROs as such are almost never audited. The licence holder is fully responsible for the product and all studies or processes that have been carried out. The drug authority is not responsible for the product.

Even a marketing licence from EMEA or United States FDA does not imply that the responsibility has shifted to the authority. Criticism in this regard (raised by the Hudson Institute or originator manufacturers) is not justified. The quality of a product can not be assessed, tested or inspected into the product, but it has to be built into it!

In other words, the manufacturer itself must have the right attitude to produce high-quality products

As is evident to WHO, CROs should have been checked before, but if a manufacturer really tries to save on quality or tries to cheat, it always will find a loophole. Only regular controls will identify these manufacturers in the end.

Was the communication/guidance poor?

The WHO recommendation of 19 November 2004 explained the background of the withdrawal and provided all necessary information for DRAs, programme managers, prescribers and patients.

It recognized the fact that not all DRAs require bioequivalence studies and therefore these DRAs were not legally obliged to withdraw the marketing authorization.

It recognized further that alternative prequalified supplies might be unavailable and recommended action. United Nations organizations were informed the same day as were all other organizations. Technically, all information was covered but the WHO unit did not anticipate that there was still need for further clarification, e.g. how to proceed in specific situations. Particularly at the level of programme managers and prescribers, clearer guidance would have been expected.

The consequences of the withdrawals were serious

Direct consequences:

- For example, in the United Republic of Tanzania the shipment for the treatment scale-up for the whole country was about to be received but after the WHO information was published, it was sent back to India. Start of treatment was delayed for months because alternative sources were not available. Although under option 3 (b) for programme managers it is stated that the use could be justified. In other (African) countries similar incidents happened.

Organizations such as the Hudson Institute or American Enterprise Institute used the withdrawal to attack WHO and requested Director-General Lee to resign because of the scandal.

Indirect consequences:

- The confidence in the Prequalification Project was undermined. “The good guys” have failed. The manufacturers failed because they obviously made serious mistakes and WHO because it did not detect the mistakes on time. NGOs suffered as well and originators felt confirmed in their opinion that generics are substandard.

7.2 Pitfalls and failures

The **withdrawal was necessary and justified**. In fact, the withdrawal showed that WHO handles those issues promptly and seriously.

But the external communication was still lacking. Although the technical information provided was complete, it was underestimated that in many developing countries, WHO has a much higher reputation than the local NDRA (if one exists) or even the MOH. If WHO states that a drug is potentially substandard but that it still could be used if, in the national requirements, bioequivalence is not requested, very few developing countries will leave this product on the market. The confidence of NDRAs in making their own decisions is very weak.

The internal communication also seems to be less than ideal. A regular meeting between the stakeholders within WHO is recommended, including AMDS, QSM, DIL and the relevant public relations department.

The prequalification team did such a good job at imitating stringent drug registration that WHO itself was recognized by some people as a kind of supranational regulatory authority. The prequalification team was always very well aware that WHO is not such a regulatory authority. **WHO has no legal power to issue or withdraw marketing authorization.** But the

prequalification can be an additional assessment tool for the NDRAs to register a drug.

Prepared for times of “war”?

Despite the experience gained through the withdrawals, it appears as if the QSM department is not well prepared for another incidence. Quality problems often turn up without any prior warning so that every pharmaceutical manufacturer has a set of standard operating procedures for how to deal with such a complaint.

The prequalification team together with relevant other departments (e.g. AMDS/PR) should have such a guideline in place in event of another “incident”.

7.3 Limitations

There are certain limitations within the project that should be borne in mind. These limitations are not the “fault” of the project but unavoidable restrictions. The most important ones are:

The WHO prequalification does not replace national marketing authorization and should not aim to do so. WHO is not a supranational authority.

- The prequalification, however thorough, is a spot check and cannot replace quality awareness on the manufacturer’s part.
- Consequently, the prequalification, like all NDRAs, cannot guarantee the quality of a product.

8. Conclusions

8.1 The effectiveness of the project

The success and the efficacy of the Prequalification Project are remarkable. Considerable effort has been made to prepare a thorough technical foundation. This was necessary to reach consensus but also made it easier to defend the project against criticism, particularly during the time of withdrawals.

The concept of the prequalification is clear and structured and actually a well-proven practice by stringent drug regulatory authorities.

The workload of the “mini” team is tremendous and the output in terms of dossiers assessed, sites inspected and products prequalified is high.

The inspections and assessments are carried out by a team of specialists on behalf of WHO. Due to the heavy workload there is a backlog of site inspections, dossier assessments and WHOPIR and WHOPAR reports.

This backlog is problematic and could eventually result in the following consequences:

- Procurement organizations are under pressure either to buy branded products or generic non-prequalified items (using procurement exemptions like the Global Fund option C);
- Donor organizations accept exemptions to meet the demand;
- Manufacturer lose hope because of the long application duration and less assistance than was received earlier;
- Programme managers delay the start of therapy if products are not prequalified (e.g. paediatric fixed dose formulation).

8.2 Sustainability

The Prequalification Project is drastically underfinanced and understaffed. Its financial sustainability is far from secured. The next biennium will prove whether WHO follows the requests of the 57th World Health Assembly dated 22 May 2004, where WHO was asked to strengthen its key role in providing technical leadership, including the strengthening of WHO’s Prequalification Project.

The demand for prequalified drugs is increasing rather than declining or levelling off. There is a priority need for second-line treatments and paediatric formulations. Furthermore, numerous re-inspections are going to be expected in 2006/2007.

The audits and assessments rely on the goodwill of DRAs that “donate” inspectors for the project. There is already a shortage of inspectors and assessors and it is most likely that the situation will get even worse.

Furthermore, the permanent heavy workload for the WHO prequalification of diagnostics and medicines could lead to frustration, so that highly skilled employees could leave. If the human resources of the team and external inspectors are not increased, the future of the project is at risk.

9. Recommendations

9.1 Priority should be paid to the following aspects

Securing the budget

To “copy” the mechanism of a stringent drug authority and carry out site inspections and assess dossiers is an expensive enterprise. Sustained funding for internal and external staff and travel allowances is crucial to maintaining these services.

The approved budget for the biennium 2006/2007 has been almost doubled compared to the previous biennium (US\$ 8.9 million vs. US\$ 4.7 million). Nonetheless, the *regular* budget has been cut and the total budget is still smaller than estimated in the business plan developed by the Clinton Initiative²². The Clinton study estimates the need – depending on implementation of certain recommendations – to be between US\$ 11.3 to 15.1 million for the next biennium.

It is now up to the prequalification team, with assistance from the HIV/AIDS Department, to raise external funds, e.g. to obtain support from donors such as the Bill and Melinda Gates Foundation. As fundraising is very time-consuming and the prequalification team has neither the time nor the skills for this, the prequalification team should be supported in this regard. AMDS could offer their assistance.

One other option, which was to charge the manufacturer itself, has been ruled out for now, since WHO is afraid that smaller generic manufacturer cannot afford such an investment. However, this discussion should be put on the agenda again at a later stage as it is common practise of all NDRAs to charge for inspections and registrations. Pharmaceutical manufacturers are profit organizations – whether generic or brand name. Why should they not contribute to the costs involved?

Reducing/shifting the workload

The Clinton Foundation Study gives some clear recommendations to improve the output by screening the applications, thereby increasing the efficacy and reducing cost per assessment. Furthermore, political commitment from EMEA and individual states from the EU -, ICH - or PIC/S - countries should be aimed for. Memorandums of Understanding should be reached to guarantee access to inspectors. Support from EMEA Art. 58 and a mutual recognition of FDA tentatively approved and WHO prequalified drugs could add a tremendous amount of authority.

Prioritization of drugs

There are two particularly vulnerable “medicines issues” in the near future regarding scaling up of ART. The first is the shortage of paediatric formulations, in particular of fixed dose combinations. FDC for children are extremely important as compliance in children is directly related to easy and pleasant treatment schemes. Unfortunately, there are currently no paediatric FDCs that are prequalified.

²² *A Business Plan for the Prequalification Programme 2006–2007* by the Clinton Foundation HIV/AIDS Initiative, September 2005.

The second is the shortage of generic second-line treatments. Due to a limited number of patients currently being treated on second line, there is a limited variety of prequalified second-line treatments. The prequalification team should seek a more proactive way to accommodate these needs, e.g. a fast-track approval. A similar approach has been followed by the “orphan drug” programme of the European drug authorities.

Since the prequalification is a technical issue, guidance on which drugs or which group of drugs should be put on a fast track should be given by a treatment-focussed department, e.g. AMDS.

1 Strengthening local capacity

A strong prequalification project needs partners on equal terms. The support for NDRA should be strengthened. Only the NDRA has the authority to withdraw a product from the market and can monitor pharmacovigilance much better than a distant authority.

2 Improving regular communication

Regular meetings, not only in times of crisis, are advisable for the departments AMDS, QSM and DIL. This would improve the information flow between the departments. Various sides suggested that the prequalification team play a more active role. If a more proactive role of the Prequalification Project and the diagnostics and lab technology unit is expected, they must be informed and involved in current treatment-related developments to enable them to better carry out their work. AMDS could play an important role in coordinating this process and scheduling the meetings.

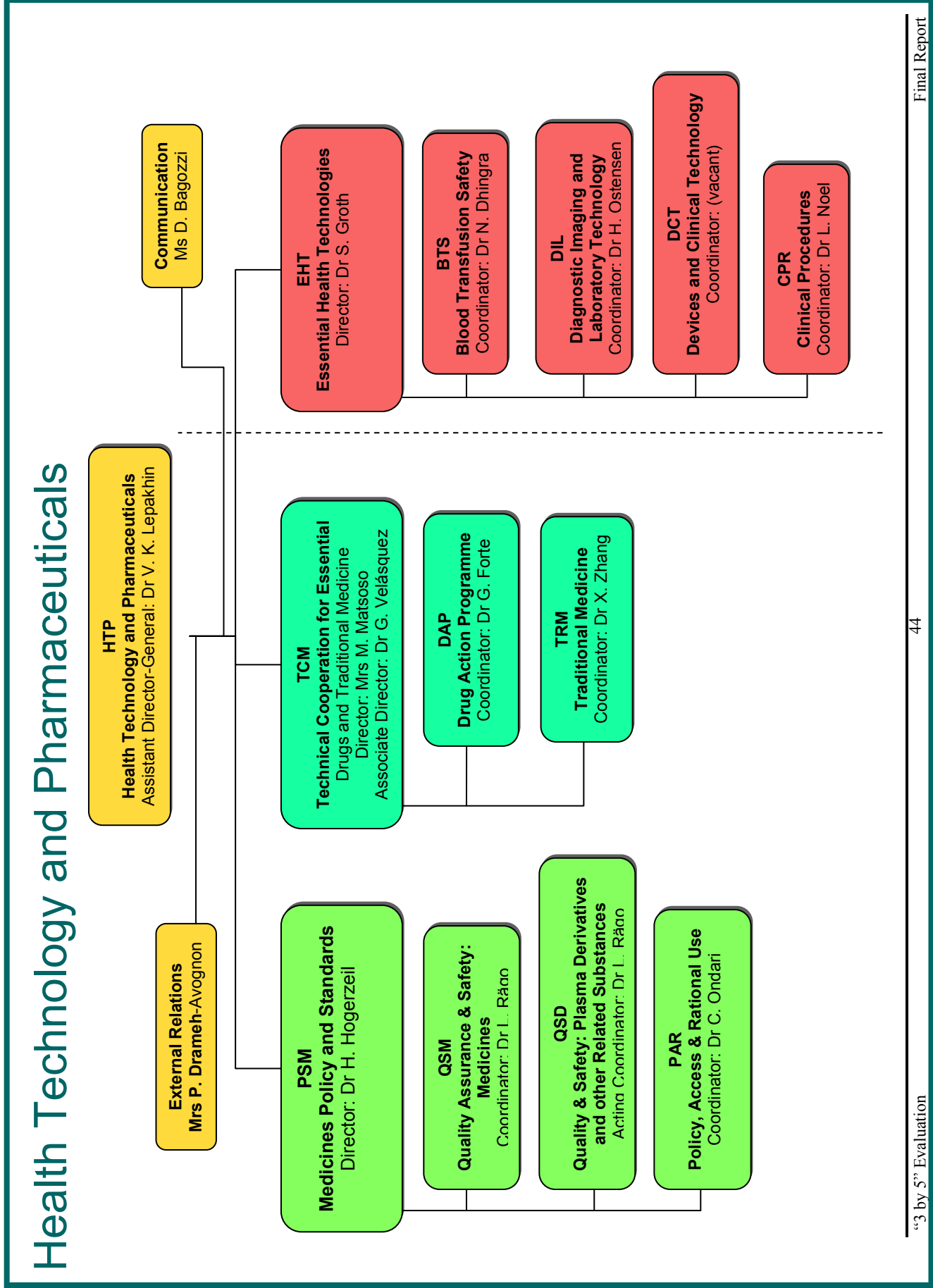
3 Diagnostics and lab technology

The focus of this study was the prequalification of medicines against AIDS/HIV. Therefore, the assessment of diagnostics and lab technologies is under represented in this report. Diagnostic and monitoring of HIV/AIDS patients with simple, robust and cost-effective techniques will be one of the major challenges for the coming years. Consequently, WHO should ensure that Essential Health Technologies (EHT) and the relevant subdivisions like DIL obtain the necessary support to fulfil their tasks.

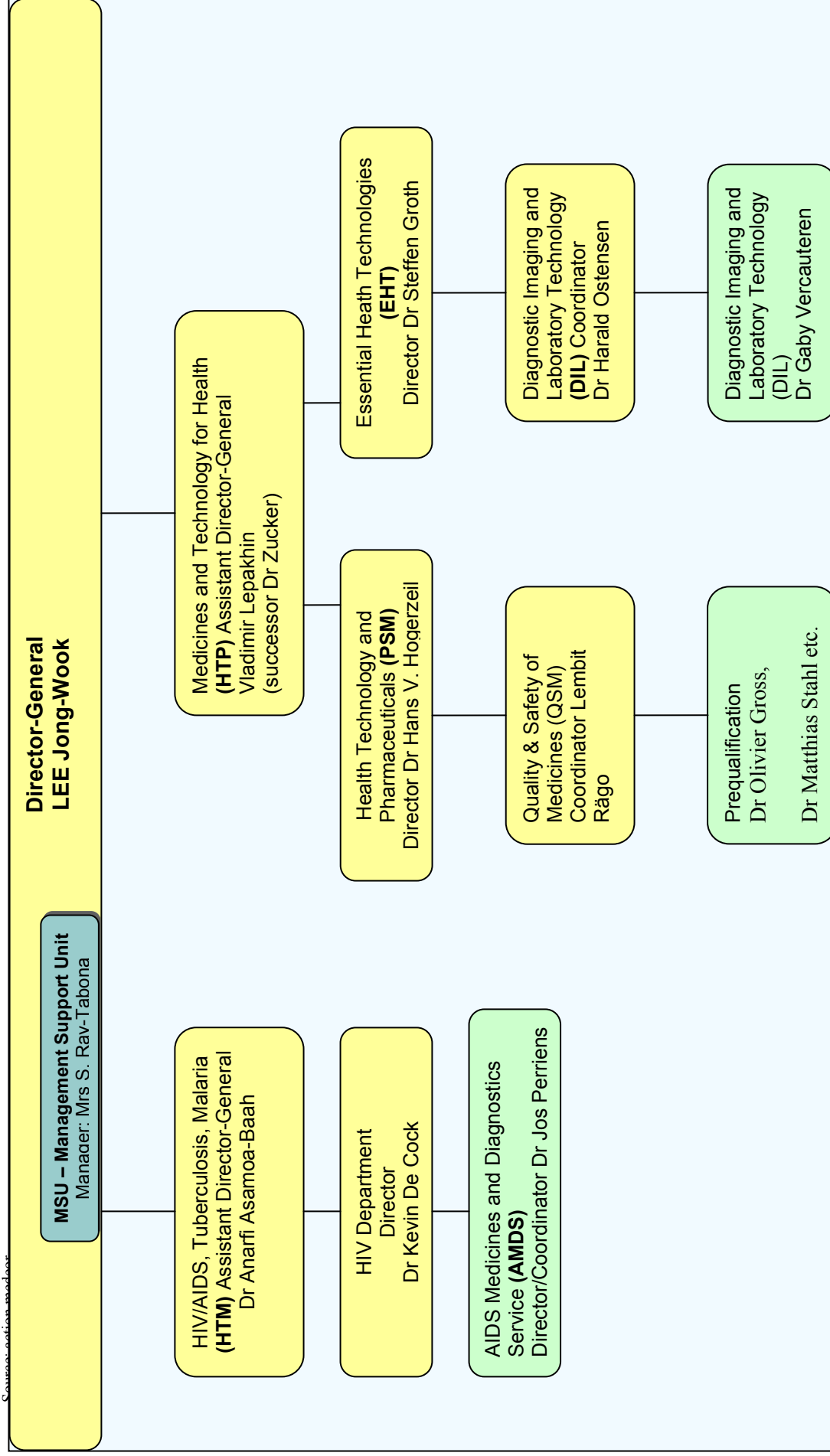
Annex A: List of individuals consulted

Title	Surname	First names	Position	Organization
	Bagozzi	Daniela	Communication Officer	WHO headquarters
	Bak Pedersen	Hanne	Chief Pharmacist	UNICEF Supply Division
Dr	Brandl	Rainer	MD HIV Treatment Program Makete Region, the United Republic of Tanzania	EAWM Austria
	Cress	Sandra	Country Director, United Republic of Tanzania	Clinton HIV/AIDS Initiative
Dr	Fink-Anthe	Carola	Communication	Boehringer Ingelheim
Dr	Giger	Urs	GMP Consultant	
	Graaff	Peter	Scientist AMDS	WHO headquarters
	Gruppelaar	Nienke	Product Manager	IDA- HIV/AIDS Group
Dr	Kopp	Sabine	Pharmacist	WHO headquarters
	Lekashingo Msuya	Emma	Pharmacist – Care & Treatment Unit	Ministry of Health – United Republic of Tanzania
Dr	Li Bassi	Luca	Procurement Officer	GFATM
Dr	Martínez	Fernando Pascual	Pharmacist	MSF Campaign for Access to Essential Medicines
	Msemu	Christopher	Director of Pharmaceutical & Technical Service	Medical stores department United Republic of Tanzania
Dr	Perriens	Joseph	Director AMDS	WHO headquarters
Dr	Rabbow	Michael	Accelerated Access Initiative	Boehringer Ingelheim
Dr	Rägo	Lembit	Coordinator QSM Department PMS	WHO headquarters
	Sands	Anita	EHT/DIL	WHO headquarters
	Shija	Rose	Essential Drugs and Officer	WHO United Republic of Tanzania
	Sigonda	Margareth	Director	TFDA United Republic of Tanzania
Dr	Thiam	Lamine	"3 by 5" Team Leader, United Republic of Tanzania	WHO United Republic of Tanzania
Dr	Vercauteren	Gaby	EHT/DIL	WHO headquarters
	Wenderlein	Dieter	Pharmacist	S'Egidio

Annex B: Organigram (HTP)



Annex C: Partial overview of WHO Organigram



Annex 9.2:

**HIV drug resistance
prevention, surveillance,
and monitoring**

FOCUS STUDY ON WHO'S EFFORTS TO ESTABLISH A GLOBAL STRATEGY ON HIV DRUG RESISTANCE PREVENTION, SURVEILLANCE, AND MONITORING

Public Health Consultants
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This study and associated documents are the property of WHO and were developed in partnership with WHO and the "3 by 5" Evaluation Team.

The findings, interpretations and conclusions expressed here are those of the authors and do not necessarily reflect those of the Evaluation Team.

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The authors thank the staff of WHO and the various medical and public health professionals who provided information critical to the preparation of this report. A list of people consulted appears in Annex 1.

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
AMDS	AIDS Medicines and Diagnostics Service, WHO
ART	Antiretroviral therapy
ARV	Antiretroviral
CDC	United States Centers for Disease Control and Prevention
CDS	Communicable Diseases Cluster, WHO
GAP	CDC Global AIDS Program
Gates	Bill and Melinda Gates Foundation
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
HIV	Human immunodeficiency virus
HIVDR	HIV drug resistance
HIVResNet	HIV Resistance Network
MOH	Ministry of Health
MOU	Memorandum of understanding
OPEC	Organization of Petroleum Exporting Countries
PEPFAR	President's Emergency Plan for AIDS Relief
SIR	Strategic Information and Research Unit, HIV Department, WHO
STAC	Strategic Technical Advisory Committee on HIV to WHO
TA	Technical assistance
TAP	Treatment Acceleration Program, World Bank
UNITE-MORE	UNITE-MORE Project, University Medical Centre Utrecht, Netherlands
WHO	World Health Organization
WR	WHO Representative (country level)

1. Introduction

This report is one of three focus studies undertaken to supplement the external evaluation of WHO's contributions to the global scale-up of access to ART for people infected with human immunodeficiency virus (HIV). This focus study examines the role and activities of WHO in developing and implementing a global strategy to address HIV drug resistance prevention, surveillance and monitoring. The study was carried out over a limited amount of time. The resulting report therefore is not comprehensive; however, consistent themes of accomplishments and lessons learnt emerged and are presented here.

Relevance of HIV drug resistance to global scale-up of ART

HIV strains with specific mutations have the ability to enter human cells and multiply in the presence of HIV drugs (virus is “drug resistant”), which diminishes or eliminates the effectiveness of specific HIV drugs. This leads to poorer health outcomes for individuals. If drug-resistant HIV is transmitted to others, treatment options for drug-naïve patients become limited as well. Thus, there are individual and societal health costs to the emergence of HIV drug resistance.

Great efforts have been made to make first-line ARVs financially accessible to resource-limited countries. Second-line drugs are still only available at prices paid in the United States and Europe. Minimizing the emergence of drug-resistant HIV will maintain the effectiveness of first-line ART as long as possible and defray the economic cost of switching to a second-line regimen.

ART is being scaled up in resource-limited countries. Emergence of drug resistance in this setting is inevitable for the following reasons:

- HIV treatment is lifelong;
- HIV has a high mutation rate; and
- HIV has a high replication rate.

The occurrence of drug-resistant HIV in ART scale-up countries is not a question of “if,” but “when,” “where,” and “among whom.” Minimizing and delaying the emergence of drug resistance will also minimize and delay the health and economic costs associated with it.

In the same way that limited resources prevent HIV drugs from being prescribed on an individual basis in many countries, so too must HIV drug resistance be monitored at the population level. The population-based public health approach (PHA) to monitoring HIV drug resistance has different goals than an individual medical approach and requires strategic, rather than convenience sampling to obtain information for treatment and programme decisions at the *population level*.

The intrinsic characteristics of HIV that lead to drug resistant strains cannot be altered. However, there are many programmatic components that can be monitored and controlled to minimize the emergence of drug resistant HIV. High-quality drugs consistently available to patients who receive HIV prevention messages and are adherent to prescribed regimens help limit HIV drug resistance.

Sustaining access to effective ART will soon be as important as *scaling up* access to ART. According to Havlir and Hammer,²³ “Brazil is already facing this challenge, and African and Asian countries with far fewer resources will probably encounter even greater hurdles in gaining access to second-line therapies.” HIV drug resistance is a critical consideration in ART scale-up efforts.

²³ Havlir DV, Hammer SM. Patents versus Patients? Antiretroviral Therapy in India. *New England Journal of Medicine*, 2005, 353:749-51.

2. Methods

The terms of reference in Annex 2 served as the basis for the evaluation methodology. While there are outcome measures included in the terms of reference, this is primarily a formative evaluation of the initial stages of WHO's efforts to develop and implement a global HIVDR strategy.

Country-specific HIVDR Programme information was obtained for the eight countries selected by the external "3 by 5" Evaluation Team for an in-depth assessment. Information was obtained via key informant interviews and document review. Face-to-face interviews were conducted with WHO headquarters HIVDR Programme staff, HIV department staff; telephone and e-mail interviews were conducted with regional WHO staff, WHO "3 by 5" officers, external evaluation team members and external programme partners, including CDC and PEPFAR. Documents reviewed included programme materials, WHO country profiles, HIV department technical assistance documentation, web sites and budgetary reports. The external Evaluation Team conducted surveys of "3 by 5" officers and national HIV/AIDS programme directors; and selected results from these surveys were reviewed for this focus study. A complete list of people interviewed and documents reviewed is included in Annex 2.

3. Description of the WHO HIV Drug Resistance Programme

The goal of the WHO HIV Drug Resistance (HIVDR) Programme is to implement an integrated global, regional and national strategy to prevent the emergence and transmission of HIV drug resistance; disseminate information to support policy and public health action; and support good ART programme practices. WHO seeks to implement this strategy through the following efforts:

- developing normative materials, including a comprehensive HIVDR “essential package” for prevention, surveillance, monitoring, dissemination of information, and evidence-based public health action to complement ART scale-up and HIVDR research efforts;
- communicating and promoting this HIVDR essential package to country, regional and global partners;
- providing technical assistance;
- developing an integrated set of HIVDR database applications for national, regional and global use;
- establishing a quality assured global genotyping laboratory network; and
- coordinating and mobilizing WHO HIVResNet and other partners to implement the above activities.

Table 1
Evolution of the WHO HIV Drug Resistance Programme

Date	Event
April 2000	IAS and WHO co-create HIVResNet, consisting of five working groups, at a meeting in Rome
2001-2002	HIVResNet approaches WHO to take leadership role on global HIVDR; HIVResNet Epidemiology Working Group produces first version of HIVDR surveillance strategy focusing on treatment-naïve populations
2001	Initial HIV drug resistance activities occur in the Communicable Diseases Cluster (CDS) at WHO
June 2003	Silvia Bertagnolio appointed (and supported by Italian Government) by WHO in the Communicable Diseases Cluster (CDS) to work exclusively on HIV drug resistance
September 2003	Donald Sutherland seconded by Health Canada at WHO in HIV Department and works on HIVDR among other responsibilities, begins developing normative materials
December 2003	<p>“3 by 5” Initiative is announced; WHO states it needs to “strongly support” a global ARV-resistance surveillance strategy</p> <p>Draft guidelines for HIV drug resistance surveillance posted on WHO web site</p>
October 2004	<p>HIVDR activities moved to Strategic Information and Research Unit in the HIV Department, Donald Sutherland assigned (and supported by Health Canada) as team leader of the new HIV Drug Resistance Programme, which includes two full-time professional staff (Sutherland and Bertagnolio)</p> <p>First “3 by 5” officer training on WHO HIVDR Strategy takes place in South Africa</p>
April 2005	Second “3 by 5” officer training on WHO HIVDR Strategy takes place in the Congo
July 2005	Country-level HIVDR monitoring and surveillance protocols drafted
September 2005	HIVDR country-level strategy conceptualized as the HIVDR “essential package”
December 2005	<p>HIVDR Programme moved to Treatment and Prevention Scale-Up Unit within HIV Department</p> <p>WHO convenes global experts to arrive at consensus on a HIVDR laboratory strategy</p>

The WHO HIVDR Programme was created in October 2004, subsequent to the announcement of the “3 by 5” Initiative in December 2003. Dr Donald Sutherland was assigned as its team leader and continues in that role. A total of two to three full-time professional staff members have been responsible for the programme, although funding for the third position is still being negotiated with the CDC.

Important to note is the relatively late entry of the formal HIVDR Programme in relation to the announcement of the “3 by 5” Initiative and general ART scaling up activities in general. The programme is faced with developing an economically and logistically feasible public health strategy for resource-limited countries to address HIV drug resistance, a highly technical issue. Implementing the strategy is complicated by the challenge of convincing countries to invest in activities that have greater long-term than short-term benefits. These long-term benefits are, however, critical to the sustainability of universal ART access efforts.

4. Evaluation findings by area

4.1 Internal programme development and management

Strategic plan for WHO HIVDR activities

- A strategic plan exists, but is not well documented;
- There is no formal operations research plan, but the programme essentially “learns as it goes” and functions well given the inherently dynamic environment of the HIV drug resistance area.

The HIVDR Programme at WHO headquarters could benefit from a strategic planning process that articulates programme direction. The forward-thinking perspective of even an abbreviated strategic planning process could provide a framework to help the programme stay abreast of the dynamic nature of the global universal access programme and the HIVDR field. However, it is understandable that this has not been a priority, given the need to rapidly develop and begin implementation of the programme. Elements of the 2005 Gates proposal have the potential to serve as the basis for a strategic plan.

Policy and guidelines for delivering HIVDR technical assistance

- No formal policies or guidelines exist;
- What does exist is an understanding among HIVDR staff for regional coverage, roughly based on language skills;
- The list of “3 by 5” focus countries serves as basic means of prioritization;
- WHO HIVResNet members are utilized for laboratory technical assistance, but no systematic procedures for tapping the expertise within ResNet exist.

The programme could benefit from a more systematic approach to providing technical assistance. Given the lack of resources available and the potential technical assistance demand from countries scaling up ART, it may become critical to have a priority-setting process in place. HIVResNet expertise has been successfully utilized as a technical assistance resource and HIVResNet members appear very willing to help provide global technical assistance. However, a systematic approach to mobilizing HIVResNet, may contribute to a more efficient use of this important resource.²⁴ Better documentation of the approach being used is also required.

Coordination within WHO

- HIVDR is verbally supported within the HIV Department;
- Efforts are made to include regional staff in technical assistance missions;
- HIV Department organizational structure frequently changes;
- STAC recognizes the importance of HIVDR in the context of ART scale-up and agrees with the global strategy the HIVDR Programme has adopted;
- Despite verbal support, there seems to be a lack of integration into larger “3 by 5” efforts (e.g. country profiles, regular communication with AMDS and other areas);

²⁴ HIVResNet representatives were unavailable to provide further insight into the interactions between WHO and HIVResNet.

- Coordination among programme staff appears to be challenging because WHO HIVDR programme staff are overextended and tend to “never be in the same place”;
- Lack of integration of HIVDR into broader “3 by 5” efforts.

Better communication and coordination between WHO HIVDR programme staff would facilitate greater efficiency of programme efforts. There is little evidence of the internal support the HIVDR global strategy receives at WHO. HIV Drug resistance is mentioned in one sentence in the June 2005 Update on the “3 by 5” Report²⁵ and little information about HIVDR appears on any WHO-related web sites. For example, the October 2005 version of WHO’s patient monitoring guidelines for HIV and ART fails to mention HIV drug resistance in a substantive manner and attention to viral load laboratory tests – a useful proxy for monitoring drug resistance – is only peripherally included.

Routine data elements collected on country ART programme profiles do not include HIVDR activities, and no regular communication occurs between the HIVDR Programme and related programmes, such as the AIDS Medicines and Diagnostics Service and the Regional and Country Coordination Unit as well as adherence efforts within its Treatment and Prevention Scale-Up Unit, HIV Department.

Human and financial resources dedicated to WHO HIVDR Programme

- HIVDR programme staff has been rushing to develop and implement a global programme on a very short timeline; they are overextended as a result of the amount of work required to initiate a global public health strategy.
- Despite WHO’s stated “strong support”²⁶ for global HIVDR surveillance, there are insufficient human resources available to provide sufficient programme infrastructure to develop global operations.
- The devotion of staff time to HIVDR strategy development and implementation has resulted in insufficient programme infrastructure.
- No staff member is dedicated to functions such as pursuing external financial support, documenting programme activities, integrating activities with related WHO programmes and maintaining a web site with up-to-date programme activities and materials.
- External support is used to fund key programme positions, including the programme leadership position.
- External partners who rely on WHO for global coordinating role view the WHO HIVDR Programme as lacking sufficient personnel for the “start-up” phase of implementing a global strategy.

Overall support for HIVDR resistance is inadequate, especially in this early development and implementation stage of the project. The lack of human resource to support activities such as grant writing and maintaining an up-to-date web site is having a negative impact on the programme’s ability to develop a viable, sustainable infrastructure and will limit its ability to implement the programme. As examples, the only normative materials available on the WHO web site are the (out of date) 2003 draft guidelines for surveillance of HIV drug resistance.²⁷

²⁵ Online WHO publication: *Update on “3 by 5” Initiative*, June 2005. <http://www.who.int/3by5/fullreportJune2005.pdf>.

²⁶ Online WHO publication: *How will the “3 by 5” initiative deal with HIV drug resistance?* http://www.who.int/3by5/publications/briefs/drug_resistance/en/index.html.

²⁷ Online WHO publication: *Guidelines for surveillance of drug resistance* (2003 draft document for review) http://www.who.int/3by5/publications/guidelines/en/resisguide12_12.pdf.

Attempts to apply for external funding from the Gates Foundation were delayed due to staff being overextended.

The programme is heavily dependent on a key leadership position for advocacy and for leveraging existing global resources to advance programme goals. The stability of this position is critical to the programme's successful continued implementation.

The perception that there are not enough personnel available for implementing a global public health HIVDR strategy is shared by informants within and external to WHO.

Recommendations - *Programme development, management and coordination*

- A HIVDR strategic plan should be developed that articulates the programme's approach to implementing a global HIVDR programme and identifies priorities. A strategic plan will provide a framework for navigating the rapidly evolving environment in which the programme operates.
- Technical assistance delivery policies and guidelines should be developed to establish a more systematic approach to delivering technical assistance. This should cover an approach to both *internal* and *external* technical assistance resources to maximize the effectiveness of all of such resources.
- An additional staff position should be added to the headquarters' HIVDR Programme with responsibility for programme elements such as facilitating integration of HIVDR concepts and activities into broader ART scale-up efforts throughout WHO; maintaining HIVDR programme documentation; maintaining the programme web site; and grant writing. Failure to provide for these types of activities will limit the programme's short- and long-term effectiveness and thus compromise the overall success of universal ART access.
- The programme director position should be supported with a stable source of funds and should not depend on time-limited, external funding. Vacancies or rapid turnovers in this position would have a major negative effect on WHO's ability to provide global HIVDR leadership and the programme's ability to maintain a global network of expertise and partners.
- After WHO HIVDR programme elements are established, investment in the WHO HIVDR programme infrastructure can be scaled back to a level sufficient to *coordinate* and *update* the HIVDR programme elements.

4.2 Global HIV drug resistance strategy

Strategy development

- WHO sought and incorporated input from external partners in all aspects of development of its global HIVDR strategy.
- WHO HIVDR strategy praised by internal and external informants.

WHO collaborated with global experts and partners to formulate a global strategy for surveillance and monitoring of HIV drug resistance as part of countries' ART scale-up plans. The strategy includes using locally generated data for local public health and ART programmatic action; local data also will contribute to regional and global HIVDR surveillance and monitoring. All focus study informants agreed with the strategy. WHO's approach was also praised by external sources for learning from the WHO Tuberculosis Drug Resistance Programme.

WHO's strategy is the only population-based approach for addressing HIVDR locally and globally; development of this strategy was essential.

Table 2
Summary of WHO's contribution and role in the area of HIV drug resistance (HIVDR)

Planned specific activity	Status at end of 2005	Impact on establishment of a global HIVDR strategy
<i>Conceptualize global public health strategy to address HIVDR in context of ART scale-up</i> Economically and logistically feasible approach for resource-limited countries; strategy developed in consultation with global experts; produce data for local public health action	Completed; global partners and technical experts are in agreement with approach	Only "population-based" approach in existence for monitoring HIVDR locally and globally: very useful
<i>Develop normative implementation materials (HIVDR "essential package")</i> Country-level guidance for HIVDR surveillance, monitoring, and dissemination of information to support evidence-based public health action related to minimizing HIVDR	"Essential package" developed to guide integration of an HIVDR programme into countries' existing ART scale-up activities; draft HIVDR monitoring and surveillance protocols developed	No countries have fully implemented HIVDR programme yet. Materials very useful, but little impact to date.
<i>Communicate and promote HIVDR "essential package" to country, regional and global partners</i> Generate understanding and support of global HIVDR public health strategy; demonstrate need for strategy; demonstration projects	Presentations at HIV conferences; trainings for 'WHO regional staff and in-country "3 by 5" officers; assistance enlisted from HIV ResNet; direct communication with CDC, PEPFAR and other partners; minimal coordination with related WHO programmes; demonstration projects underway	<ul style="list-style-type: none"> • Communication and promotion useful, but greater accessibility and dissemination is needed (e.g. web site; dedicated regional staff) • Demonstration projects very useful, but still in progress
<i>Provide in-country programmatic and laboratory technical assistance</i> Leverage existing programmes and knowledge in countries; tailor assistance to needs of specific country	Technical assistance provided to many countries; headquarters staff operating at unsustainable levels; HIV ResNet mobilized for lab technical assistance; countries found technical assistance helpful	Useful; but greater supply is needed to achieve greater impact
<i>Develop integrated set of HIVDR database applications for national, regional and global use</i> Standard system for data entry and analysis at country level; can be aggregated at region and global levels; standard reports for making public health decisions related to HIVDR	No database applications fully developed; funds are dedicated but production lags behind countries' readiness	Potential impact is significant, however no impact to date
<i>Establish global genotyping laboratory network</i> Quality-assured, standard HIV genotyping services; aim for country or regional service base	No laboratory network exists yet; consensus strategy for global HIVDR laboratory strategy in process; good use of global experts	Potential impact is significant, however little impact to date

4.3 Country-level HIV drug resistance guidance

- An HIVDR "essential package" has been developed that provides countries an outline for integrating an HIVDR programme into ART scale-up activities.
- Draft HIVDR monitoring and surveillance protocols have been developed.
- Demonstration projects are underway for integrating the HIVDR "essential package" into the ART scale-up plan of a few countries (e.g. India, Kenya and Malawi).
- The actual use of guidelines and tools is limited, but expected to expand.

The methodology and approach outlined in these documents are scientifically sound and appropriate for implementation in resource-constrained countries; informants routinely praised the methodology. The guidelines and protocols were developed in consultation with external partners with appropriate expertise. They provide a practical approach to implementing an HIVDR prevention, surveillance and monitoring strategy in resource-limited areas that appears feasible to implement without detracting substantively from other essential ART scale-up activities.

Recommendations – Country-level HIV drug resistance guidance

- Current HIVDR guidelines and example protocols should be maintained on the WHO web site to ensure that interested parties have access to current normative materials. Efficiently disseminating guidelines and tools is critical to implementing a global HIVDR strategy in a timely manner.

4.4 Communication and promotion of global strategy

HIVDR staff has done an excellent job communicating with international partners via presentations and networking at international meetings.

- Some effort has gone into HIVDR programme participation in regional ART scale-up trainings and “3 by 5” officer trainings.
- Lack of integration of HIVDR activities into related WHO ART programmes represents a missed opportunity for additional communication and promotion of HIVDR strategy.
- Support for guidelines within and external to WHO appears to be excellent.
- The Internet is under-utilized for communicating and promoting WHO’s HIVDR strategy.

Communication and promotion of WHO’s HIVDR global strategy has largely been successful. All global, regional and national partners contacted were well aware and supportive of the WHO approach. However, communication could be enhanced through better utilization of the Internet. Neither current versions of country-level guidance and protocols nor updates on demonstration projects are available on the WHO web site.

Good progress has been made in promoting WHO’s HIVDR strategy at the country level, considering the short time the programme has been in existence. However, internal and external informants indicated that the actual rate of countries engaging in HIVDR activity planning is too slow. Better integration with existing WHO ART scale-up programmes is needed.

Recommendations – Communication and promotion of global strategy

- In addition to the availability of country-level HIVDR guidance and protocols, updates on demonstration projects should also be provided on the WHO web site to publicly document progress toward programme goals.
- Regional WHO staff should be leveraged more to promote WHO HIVDR strategy at country level.
- Better integration with ART-related WHO programmes (e.g. AMDS, IMAI) should be sought to enhance communication and promotion of WHO’s HIVDR global strategy.

4.5 Technical assistance

The complexities and technical nature of the HIVDR essential package coupled with the demands associated with planning and implementing ARV make it unlikely that countries will be able to plan and implement the HIVDR essential package without some type of technical assistance – either from WHO or a collaborating partner (e.g. the CDC). Implementation of a global HIVDR strategy is therefore dependent on implementing a successful technical assistance strategy.

Technical assistance may involve guidance in plans for incorporating the WHO HIVDR essential package into country ART plan, consultation on laboratory facilities/processes, and help with writing HIVDR activities into grant applications to the ‘Global Fund’ or other monetary sources.

- Since the inception of the WHO HIVDR programme, 23 countries have requested HIVDR technical assistance.
- Between January and September 2005, technical assistance was provided to 22 countries, including 3 that specifically requested laboratory technical assistance.
- HIVDR programme staff providing technical assistance is operating at unsustainable levels.
- WHO HIVResNet appears to be under-utilized and is not mobilized for programmatic technical assistance.

The WHO HIVDR programme receives requests from countries for HIVDR technical assistance. Currently, the programme is able to provide timely technical assistance to countries by mobilizing WHO HIVDR programme staff and/or HIV ResNet members. Only one requesting country had to be turned away; the reason for denying the technical assistance was that it was not a “3 by 5” focus country. Of the 22 countries provided technical assistance 15 have integrated a portion of or have active plans to integrate the WHO HIVDR essential package into the country ART programme.

All six countries consulted for this evaluation reported a high level of satisfaction with the technical assistance they received from WHO headquarters staff. Countries reported internal obstacles to implementation that are independent of HIVDR technical assistance needs.

The capacity of the WHO HIVDR Programme staff is exceptional. They are all extremely motivated and dedicated to implementing the WHO HIVDR global strategy. The technical assistance accomplishments to date, in terms of countries reached and apparent quality of the assistance is commendable. However, the staff is stretched thin and the current pace of work is not sustainable.

As scale-up efforts continue, the demand for in-country HIVDR technical assistance will surpass the capacity of the WHO HIVDR programme to *provide* and *document* assistance unless HIVResNet and/or other resources are utilized more effectively. Other creative approaches to providing technical assistance may need to be developed (e.g. fund a regional office position dedicated to HIVDR activities).

Recommendations – *Technical assistance*

- Implementation of a global HIVDR strategy is dependent on implementing a successful technical assistance strategy. Increasing the use of existing resources, such as WHO HIVResNet members and CDC GAP in-country expertise should be explored.
- Building the HIVDR technical capacity at WHO regional offices should be considered.

- In addition to the availability of country-level HIVDR guidance and protocols, updates on demonstration projects should also be provided on the WHO web site to leverage “lessons learnt” for countries that subsequently initiate HIVDR programmes.

4.6 HIV drug resistance database applications

Developing database applications is necessary for countries to translate HIVDR data into useful information for local public health and ART programmatic decisions. These data also will also be used to assess the status of HIVDR regionally and globally.

- No database applications have been fully developed.
- Funds are dedicated, contracts established and work to complete the national database application is underway.
- Database training for the national database application is scheduled for January 2006 in Malawi.
- It is unclear if documentation of database development and creation of comprehensive user guides were included in specifications to computer programmer.
- Some countries are ready to begin collecting HIVDR data.

The database applications seem to have high priority now, but are past due given that countries are ready to collect data now. This delay appears directly related to a lack of availability of WHO HIVDR programme staff due to competing programme priorities.

Documentation of database development and comprehensive users’ guides are critical to the functionality of a database. Too often database documentation receives little attention in the rush to meet deadlines.

Recommendations – HIV drug resistance database applications

- Implementation of a global HIVDR strategy is dependent on successful local data management. Concerted effort should be focused on producing a functional, user-friendly database system quickly.
- The database should be documented thoroughly.

4.7 Global genotyping laboratory network

Surveillance and monitoring of HIVDR requires laboratory participation. Establishment of a quality-assured HIVDR laboratory network utilizing standard procedures is critical to implementing a global HIVDR strategy.

- No laboratory network exists yet.
- A meeting of global experts was convened in December 2005 to arrive at a consensus on a strategy to develop a global HIVDR laboratory network.
- The strategy will include the following elements: network structure, function of network laboratories, selection criteria, developing a process for laboratory assessment, and selection of a quality assurance system.
- WHO genotyping laboratory meetings, with two exceptions, have occurred at other scheduled national and international meetings.

At the time of this report, no global genotyping laboratory network exists. However, given the limited duration and resources of the WHO HIVDR programme, reaching a milestone like consensus on a standard laboratory strategy will be an important achievement.²⁸

Recommendations – *Global genotyping laboratory network*

- Implementation of a global HIVDR strategy is dependent on the availability of affordable, quality-assured laboratory testing. Concerted effort should continue to be focused on establishing a global genotyping laboratory network.

4.8 Collaboration with partners

Major WHO partners in the area of HIVDR vary by country and region, but include WHO regional offices, CDC GAP, PEPFAR, UNITE-MORE, GFATM, OPEC, TAP, and various research and academic institutions.

- WHO HIVDR programme staff members have a good awareness of partners' efforts in the area of HIVDR.
- WHO global partners have a good awareness of WHO's efforts in the area of HIVDR.
- Documentation of WHO and other HIVDR activities in countries is limited.
- Multiple examples of local coordination with partners' efforts were provided by WHO headquarters staff, CDC, WHO regional offices and country informants.
- There is regular contact with HIVResNet members.
- The programme has achieved a presence at international meetings and makes efficient use of existing HIV meetings for HIVDR meetings.
- Documentation of collaborations with partners is limited.
- Coordination between headquarters and WHO Regional Office for Africa activities is limited.

Coordination with external partners has been excellent.

During interviews, WHO HIVDR programme staff listed many examples of partners' ART scale-up and HIVDR activities in many countries. The extensive professional networks of the two medical epidemiologists on staff enable them to learn quickly of new HIVDR endeavours throughout the world. This knowledge provides an opportunity to coordinate the country-level WHO HIVDR strategy efficiently with a country's existing HIV-related activities. Many WHO HIVDR programme staff indicated the value of having an up-to-date catalogue of country-specific HIVDR activities.

An example of coordination with partners' efforts in country is Kenya. WHO, CDC GAP, and the Kenyan MOH actively collaborated to begin implementing HIV drug resistance surveillance through the existing HIV disease surveillance system already established in Kenya by the MOH and CDC GAP.

WHO HIVDR programme staff (at headquarters) and the WHO Regional Office for Africa staff did not seem well-informed of the other's activities nor did HIVDR activities seem synchronized. Despite invitations to participate in technical assistance visits to the WHO African Region countries, staff in this Regional Office did not attend. WHO Regional Office for Africa staff has

²⁸ HIVResNet representatives were unavailable to provide further insight into the development of the global genotyping laboratory network.

been engaged in HIVDR activities since before the headquarters programme was initiated. The staff, which is also responsible for non-HIVDR activities, is stretched beyond capacity. At least one WHO African Region country recommended better coordination between headquarters and the Regional Office to facilitate better ‘uptake’ of the HIVDR strategy by country MOH.

The countries served by the Regional Office for Africa are generally both very poor and in very great need of ART. Scaling up ART in these areas responsibly, by including an HIVDR strategy, requires efficient coordination and leveraging of resources to promote the value and feasibility of an HIVDR strategy in countries.

The interface between WHO headquarters and WHO HIVResNet is not well-documented despite an apparently good working relationship. Documentation of all formal collaborations and coordination (e.g. MOU) would contribute to the programme’s long-term stability and transparency. Clear expectations for partners would contribute to greater collaborative efficiency.

Recommendations – *Collaboration with partners*

- Produce annual or biennial reports on the status of the global HIVDR strategy, including HIVDR data when available, to establish WHO’s leadership in the global public health approach to HIVDR, as well as, to inform stakeholders of progress made.
- Develop and maintain a simple, up-to-date and country-specific database of both WHO and partners’ efforts in the area of HIV surveillance and HIVDR activities at headquarters for use by headquarters, regional and in country staff for efficient implementation of HIVDR strategy in country. Reasonable access to other partners that could benefit from the database could be available by request.
- Better document collaborations between WHO and partners, in particular IAS (HIVResNet), and specify expectations of each collaborating entity. The WHO TB programme has examples of such documentation.
- Consider dedicating funds for a HIVDR staff person at the WHO Regional Office for Africa to facilitate coordination and leveraging of resources between headquarters and the Regional Office in implementing the WHO HIVDR strategy in WHO African Region countries.

5. Conclusions

5.1 Unique role

A population-based, public health approach to minimizing the emergence of HIV drug resistance is critical to maximize the period of time that first-line HIV drugs remain effective in the developing world. Identified by global partners as the agency with the most legitimacy as a global public health authority, WHO is in the unique position to provide the leadership and coordination necessary to address HIV drug resistance on a worldwide scale. Without such a programme it is expected that drug-resistant HIV will emerge earlier and more rapidly, leading to poorer health and economic outcomes for countries where resistance emerges.

5.2 Accomplishments

Considering the resources available to it, the WHO HIVDR programme has done an excellent job of initiating development of a global HIVDR strategy in a short period of time. Normative materials have been developed, members of the programme staff are well on their way to establishing a global genotyping laboratory network, initial work on database applications is underway, and technical assistance has been provided to 22 countries. These are significant accomplishments for the limited staff dedicated to implementing a global HIVDR strategy to maximize ART's effectiveness in resource-limited areas as long as possible.

5.3 Moving forward

The primary lesson learnt to date is that the programme should have been started earlier, with more personnel, and better synchronized with the overall "3 by 5" programme. The programme's primary challenge moving forward is a lack of resources to establish and maintain critical infrastructure while keeping up with the demands of providing technical assistance to individual countries. Addressing this challenge is likely to require a mix of seeking external support for programme activities and pursuing creative strategies to provide in-country technical assistance. The programme needs the infrastructure support so that it may be as proactive as possible in shepherding global action to address HIV drug resistance in the context of universal ART access.

Annexes

Annex 1: Sources consulted to inform this focus study (in alphabetical order)

People:

Dr Diane Bennett (WHO)
Dr Silvia Bertagnolio (WHO)
Dr Donald Sutherland (WHO)
Dr Yves Souteyrand (SIR)
Dr Guy-Michel Gershy-Damet (WHO Regional Office for Africa)
Dr Abdou Moha (Mozambique)
Dr Rex Mpazanje (Kenya)
Dr Theresa Diaz (CDC)
Dr Kassim Sidibe (CDC)
Dr Rueben Granich (PEPFAR)
Dr Eyerusalem Kebede (WHO, Ethiopia)
Dr Francoise Bigirimana (Burkina Faso)

Documents (provided by WHO HIVDR programme staff or accessed via WHO web site):

Monitoring of HIV Viral Suppression and HIV Drug Resistance in Populations Receiving ART in Resource-Limited Settings (V.07-08-05).

Various presentation files describing the WHO HIV Drug Resistance Strategy.

Agenda and presentations from a satellite symposium hosted by WHO HIVResNet and UNITE-MORE at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, 25 July 2005.

WHO HIVDR Programme biennium operating budget for 2004–2005 and proposed budget for 2006–2007.

Draft grant proposal to the Bill and Melinda Gates Foundation dated 9 September 2005.

Progress on Global Access to HIV Antiretroviral Therapy, An update on “3 by 5.” June 2005.

Web sites:

WHO
WHO regional offices
UNAIDS

Annex 2: Terms of reference - Focus study on WHO's role and activities in the HIV drug resistance area

Introduction

The global scale-up of access to ART in resource-limited countries will inevitably result in the emergence of some level of HIV drug resistance (HIVDR). Given the serious consequences of HIVDR, WHO has incorporated HIVDR prevention, surveillance and monitoring into its “3 by 5” Initiative activities.

In accordance with a grant agreement between WHO and the Canadian International Development Agency, an independent formative evaluation is being conducted of WHO's contribution to “3 by 5”, specifically in developing countries. This evaluation includes a smaller focus study on WHO's accomplishments and lessons learnt regarding its efforts to establish a global strategy on HIVDR prevention, surveillance and monitoring. This proposal describes a plan for evaluating WHO's role and activities in the area of HIVDR.

Methods

Given this focus study's time and resource limits, document review will be used as well as interviews with staff at various levels within WHO and within selected international partner and stakeholder agencies to assess WHO's actions in the following areas:

- (1) Programme development and implementation, management and coordination;
- (2) Utilization and effectiveness of guidelines and tools;
- (3) Technical support and capacity-building;
- (4) Complementarity of WHO's activities with partners' efforts.

Table 1 provides a framework for the proposed approach, including example indicators and key questions for each area. Briefly, the consultants plan to collect all available information on WHO's activities in the area of HIVDR; select up to three focus countries receiving HIVDR technical assistance from WHO; develop standard survey instruments to collect data necessary to measure the various indicators; conduct the interviews, analyse the data, and summarize the findings in a draft report by 23 December 2005.

The consultants will use existing data as much as possible. They will have the full cooperation of WHO staff, including the provision of contact information for relevant internal and external individuals at international, regional and national levels. The results of this process will allow them to meet the objectives of this evaluation and provide answers to the following evaluation questions:

- What has WHO developed in terms of guidelines and documentation?
- How effective has WHO been in mobilizing external support for its strategy?
- What was the level of technical support provided by WHO to countries?
- Has WHO's strategy been supported and implemented in the “3 by 5” focus countries?
- What are lessons learnt for the next phase of scaling up access to treatment and prevention?

Modalities of the conduct of the study

The work will be conducted by two consultants, Peter Carr and Tracy Sides, who will collaborate on this work.

Document reviews and interviews will be implemented and completed by 12 December 2005. The consultants plan to work in Geneva reviewing documents and conducting interviews between 30 November and 6 December 2005. Project data will be analysed and the findings summarized in a draft report to be submitted to the Evaluation Team by 23 December 2005.

Table 1
Evaluation framework with key questions, example indicators and data collection methods

Level	Area	Key questions	Indicator example	Method
Input		Strategic plan for HIVDR activities, including monitoring and evaluation and operations research plans exist	Internal policy and guidelines in place and in use	
		Policy and guidelines for providing HIVDR technical assistance to countries exist	Coordination mechanism in place within WHO	
Process	Programme development, implementation, management and coordination	Coordination is established within WHO and with external partners	Coordination mechanism in place with external partners	Review relevant documentation from WHO
		Infrastructure at WHO available	WHO staff dedicated to HIVDR activities	Interview HIVDR Team and other WHO staff
Output		Adequate human & financial resources dedicated to HIVDR programme	WHO resources committed to HIVDR programme	
		Guidelines and tools for implementing country-level HIVDR programme exists	HIVDR guidelines and tools in place	
Process	Utilization and effectiveness of guidelines and tools	HIVDR guidelines are accessible to and utilized by ART scale-up countries		
		Stakeholders & international partners are aware of and support WHO HIVDR guidelines	% of ART scale-up focus countries aware of WHO HIVDR guidelines	Review WHO HIVDR guidelines
Output		ART scale-up countries have an HIVDR Working Group, workplan and both are integrated into country ART plan	% of ART scale-up focus countries that have an HIVDR Working Group and tools and workplan	Interview WHO staff, selected stakeholders and partners at various levels (e.g. Secretary-General of OCEAC)
			% of selected stakeholders and international partners aware of/support WHO HIVDR guidelines for ART scale-up countries	

Table 1 (cont)

Evaluation framework with key questions, example indicators and data collection methods (cont)

Level	Area	Key questions	Indicator example	Method
Process	Technical support and capacity building	ART scale-up countries request & are provided technical assistance	Number of ART scale-up focus countries requesting HIVDR technical assistance	Review relevant WHO programme documentation (e.g. national scale-up plans on file at WHO)
		HIVDR programme technical assistance from WHO is accessible and adequate for ART scale-up countries	% of ART scale-up focus countries that received HIVDR technical assistance after requesting it	
		Laboratory technical support is accessible and adequate for ART scale-up countries	Number of national ART scale-up plans that include monitoring HIVDR Number of selected ART scale-up countries utilizing a sentinel laboratory to monitor prevalence and trends over time of HIVDR	
Output		Network of sentinel HIVDR surveillance laboratories exists	Number of ART scale-up countries that received laboratory technical support	Interview WHO staff and selected focus countries' national AIDS programme staff, as available
		HIVDR data are collected and disseminated in areas that have implemented HIVDR monitoring programme	Network of sentinel HIVDR surveillance laboratories Disseminated HIVDR data	
Process	Complementarity of WHO's activities with partners' efforts	WHO HIVDR programme staff are aware of partners' efforts in the area of HIVDR	Level of knowledge among WHO HIVDR programme staff of partners' efforts in relation to HIVDR	Review relevant WHO HIVDR programme documentation
		WHO HIVDR programme collaborates with relevant international, regional and national partners	Number and nature of collaborative activities between WHO HIVDR programme and partners	Interview WHO staff, selected stakeholders and partners at various levels (e.g. IAS, OCEAC, etc.)
		WHO efforts in HIVDR area are non-duplicative	Number of WHO HIVDR programme activities that are duplicative of partners' efforts	
Contribution		Progress made towards WHO HIVDR programme goals	Summary of programme accomplishments	Summarize findings from evaluation activities indicated above
		Lessons learnt	Comparison of accomplishments to stated programme goals and timelines Summary of lessons learnt by area of action	

Annex 9.3:

A synopsis of antiretroviral drug pricing trends

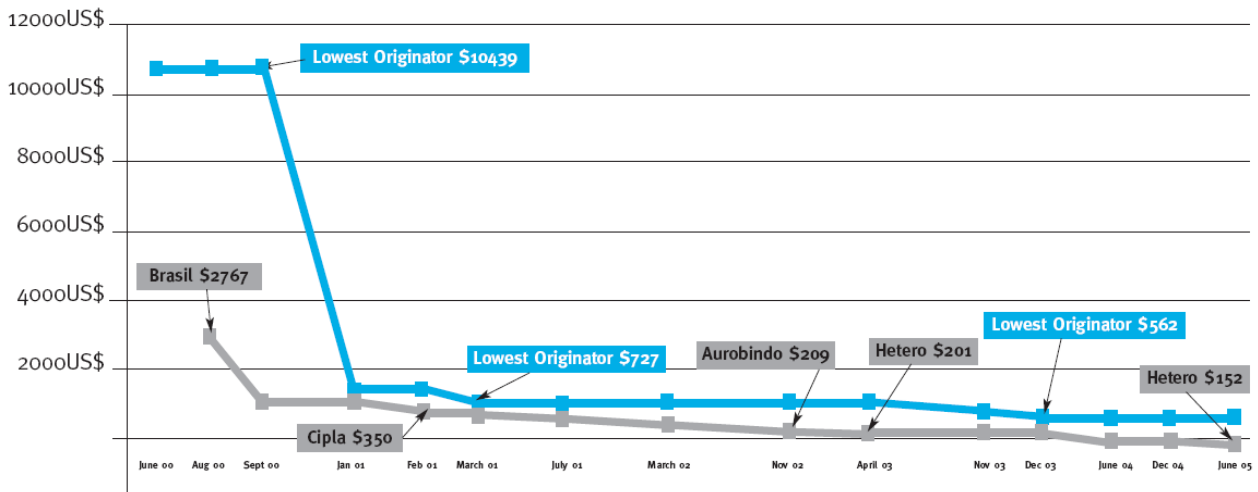
Overall trends in antiretroviral drug prices²⁹

Figure 1 below shows the effects of generic competition. The most dramatic price reductions in first-line ARV therapy occurred between 2000 and 2005. After Brazil began manufacturing its own generic ARVs, the R&D companies responded (through the Accelerating Access Initiative) by cutting their prices for sub-Saharan Africa. When Indian generic companies joined the competition, prices dropped further from US\$ 600 to US\$ 350, to the current price of US\$ 152 per year. The R&D industry has not shown an equivalent price reduction lately: since 2003 their best price has been fixed at US\$ 562. The impact of “3 by 5” on this price competition has been limited.

Fig. 1

The Effects of Generic Competition

May 2000-June 2005



Sample of ARV triple-combination: stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). Lowest world prices per patient per year. Generic competition has shown to be the most effective means of lowering drug prices. During the last four years, originator companies have often responded to generic competition.

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²⁹ This is a synopsis of findings from a focus study commissioned by the Evaluation Team, conducted by Dr Wilbert Bannenberg in December 2005.

Key points on ARV price reductions

- In 2002, WHO public health approach guidelines were published that made it possible to focus on securing a limited range of first-line ARVs.
- The World Trade Organization Doha Declaration confirmed the right of developing countries to put public health interests above trade interests: this has made it easier for more affordable generic medicines to enter the market.
- After negotiations with ARV raw material producers, the Clinton Foundation announced on 22 October 2003 a price reduction of first-line FDCs from US\$ 270 to US\$ 140. The Foundation later also announced price reductions of test kits and diagnostic equipment.
- Generic prices have fallen 47% over the past four years, from an annual figure of US\$ 285 to US\$ 151. Branded ARVs fell only 23% from US\$ 727 to US\$ 562.
- Prequalified ARVs are still about 20% more expensive than the cheapest available generic.
- FDC formulations of ARVs are now nearly priced at the same level as using combinations of single formulation tablets.
- Outside Africa, the “preferential prices” offered by R&D companies are much higher than in Africa. Generics are often not accessible due to patents.
- In Latin America, PAHO has been quite successful in dropping ARV prices through group negotiations.
- Temporary removal of several Indian generic ARVs in 2004 from the WHO Prequalification List caused serious supply interruptions, and increased ART cost since more expensive ARVs had to be used.
- Stock-outs and long lead times are increasingly seen among R&D manufacturers, since they apparently cannot cope with sharply increased demand.
- ARV production has started in many African countries, but they have not yet managed to beat prices offered by Indian manufacturers. The public health impact of this is unclear, and the quality remains largely untested (most are not yet WHO prequalified).

Future challenges to securing affordable ARVs:

- First-line ART costs will only reduce further through access to more affordable, good-quality raw materials (mainly sourced from China and India).
- First-line ARVs from the R&D industry outside Africa remain substantially more expensive than in Africa. This is due to national patent protection blocking access to the more affordable generics; higher differential price levels demanded by originator companies; and regulatory barriers. Where there are supply monopolies, higher prices are being charged for generics as well.
- Paediatric ARV formulations (liquid and solid drugs in paediatric formulations) are more expensive than those of their adult equivalents. Treating a child weighing 10 kg for one year with stavudine, nevirapine and lamivudine can cost up to US\$ 816, 448% of the cost of treating an adult with the same drugs (US\$ 182). Several dosage forms are not suitable for children, and lower-dose FDCs for children are badly needed.
- Second-line ARV prices are currently 3–12 times as expensive as first-line ART. These high prices will be a barrier for those patients who have developed resistance against the much more affordable first-line treatment.