Imagine carrying your weak and feverish child to the nearest health clinic. Imagine the doctor making his diagnosis and prescribing an expensive antimalarial drug. Reassured that treatment is effective, you hand over almost all of the family’s monthly budget to pay for the pills. Now imagine that the antimalarials that your child is given are actually nothing more than a poor-quality imitation, containing so little active ingredient that they will ultimately fail. Counterfeit or simply poor quality? The details are not important to this family — the tragic outcome is the same.

The WHO Prequalification Programme prevents this imaginary tale from becoming a reality for thousands of people every day. It does this via stringent assessment of product dossiers, inspection of manufacturing sites and of contract research organizations (CROs), prequalification of national pharmaceutical quality control laboratories (NPQCLs), and advocacy for medicines of assured quality. It is demonstrating that by making quality pharmaceutical products available, procurement and distribution of medicines are speeded up. This in turn helps to maximize treatment outcomes and use of resources.

Expanding the lists of prequalified medicines continued to be the Prequalification Programme’s principal objective in 2005. Assessments and inspections continued apace, resulting in prequalification of additional medicines for treating HIV/AIDS and malaria.

In 2005, more generic drugs were prequalified than brand-name products, illustrating the success of the Prequalification Programme in capacity building in the generic sector. This was the first time that the balance had tipped in favour of generics.

The Programme was pleased to observe that the product dossiers submitted for assessment were of a higher quality than in previous years. The improvement indicated that efforts to provide feedback and guidance to manufacturers following dossier assessments had been worthwhile.

Experts attended nine assessment sessions — each of 5 days — at the UNICEF Supply Division in Copenhagen, where the product dossiers are received and stored. Six sessions had been planned, but due to the volume of work, nine sessions were held. Product dossiers relating to products for treating HIV/AIDS, malaria and TB products were examined in each session.

A total of 52 inspections were carried out:

- 20 inspections of the manufacturing sites of finished products
- 10 inspections of the manufacturing sites of active pharmaceutical ingredients (APIs)
- 14 inspections of contract research organizations (CROs)
- 8 inspections of national pharmaceutical quality control laboratories (NPQCLs) in Africa.

An overview of inspections performed, listing manufacturing sites, CROs and NPQCLs that comply with WHO norms and standards regarding good manufacturing practice (GMP), good clinical practice and good laboratory practice, respectively, was added to the prequalification website.
Launched in 2001, partnered with UNAIDS, UNICEF and the UN Population Fund, and receiving support from the World Bank, the Programme is tackling the quality problems commonly associated with medicines for three high-burden diseases:

- **HIV/AIDS**: For people living with HIV/AIDS, antiretroviral (ARV) products offer hope of prolonged survival — yet they are not available in sufficient quality or quantity where they are needed most.
- **Malaria**: Data from a recent WHO survey in six African countries showed that 10-65% of sampled antimalarial chloroquin tablets contained too little active ingredient. The poor quality of first-line treatments is contributing to drug resistance and treatment failure.
- **Tuberculosis (TB)**: Many generic anti-TB medicines have serious quality defects, due to their poor manufacturing quality. Also, bioequivalence has often not been proved.

### Prequalification of Products for HIV/AIDS

In 2005, 22 new antiretroviral (ARV) products were prequalified. By the end of the year, the number of prequalified HIV-related products had risen to 107. (The lists of prequalified products can be found at: http://mednet3.who.int/prequal/) If US Food and Drug Administration (FDA) approvals (see New Collaboration section, page 8), are also included in this total, the figure stands at 116. The list includes 72 different ARV preparations, 16 of which are double or triple formations.

Of the 72 prequalified ARV products, 34 are from brand-name companies and 38 from generics companies. At the end of 2005, an additional 105 HIV/AIDS medicines were being evaluated.

During the nine dossier assessment sessions, 222 assessment reports on HIV/AIDS-related products were written. This figure does not include numerous “ad-hoc” assessments carried out in between the Copenhagen sessions by WHO-appointed experts. In all, 12 GMP inspections were carried out for HIV/AIDS medicines, including one three-year re-inspection and five inspections of manufacturers of ARV APIs. A total of nine inspections of CROs were conducted, corresponding to more than 20 bioequivalence studies of HIV/AIDS medicines.

### Quality control of ARVs

The Prequalification Programme continued to carry out “post-approval” monitoring of the quality of prequalified products; some of the results have been published. (See reference to *Journal of Generic Medicines* article in Publications and Information section, on page 9.) In 2005, it participated in two large sampling/testing programmes of ARV products. Focused on post-approval quality control, the studies were carried out with relevant expert authorities:

**STUDY 1**: UNICEF, the French Agency for the Safety of Health products (Agence française de Sécurité sanitaire des Produits de Santé — AFSSAPS) and WHO worked together to sample prequalified ARV products. Fifty-six samples for analysis were collected from the UNICEF Supply Division in Copenhagen or requested from the manufacturers.

**Results**: No problems with quality were found; one packaging discrepancy was noted.
HOW DOES THE PROGRAMME WORK?

The Prequalification Programme makes a solid, scientific assessment — based on WHO prequalification guidelines, that are in line with internationally harmonized standards — of the quality of both generic and patented medicines. The process begins with submission to WHO, by a pharmaceutical manufacturer, of an Expression of Interest, together with a product dossier. The safety, quality and efficacy information contained in the product dossier is examined by two WHO-appointed assessors. Both assessors must approve its contents. If they disagree, or if the product is particularly complex, additional assessors are generally consulted. When the dossier is close to approval, inspection of the manufacturing sites (of the active pharmaceutical ingredient and the finished product) is organized.

Inspection of a CRO is sometimes also necessary. Products submitted for prequalification are often multi-source generics. In such cases, therapeutic equivalence with an innovator (brand-name) product is verified by performing a bioequivalence study. Such studies are generally carried out by an independent CRO, which must therefore also be inspected and approved.

STUDY 2: The WHO Department of Technical Cooperation for Essential Drugs and Traditional Medicine (at WHO Headquarters) and the Essential Drugs Programme (of the WHO Regional Office for Africa — AFRO) worked together on analysing the quality of 440 samples of both prequalified and non-prequalified ARV products circulating on the market in Africa. The products were collected by AFRO, together with national government officers and analysed by the Swissmedic Official Medicines Control Laboratory (OMCL).

Results: Of the 440 samples tested, only 13 were found to have nonconformities, none of which were considered severe. Six products concerned the same manufacturer and some of the issues related to new packaging formats. Further ARV product samples have been collected in Africa and are being tested.

PREQUALIFICATION OF PRODUCTS FOR TB

A total of 52 assessment reports — linked to more than 50 TB products — were written during the nine Copenhagen dossier assessment sessions. Approximately 65 TB products were evaluated for prequalification. Almost 50 TB product dossiers were also reviewed by experts, to assist the Global Drug Facility, which is reviewing the quality of commonly available TB products that have not yet been prequalified.

Inspections included: five GMP inspections of TB finished product manufacturing sites; three inspections of API manufacturing sites and two inspections of CROs.

By the end of 2004, a total of eight TB products had been prequalified. However, no TB products were prequalified during 2005. This was due to continued failure of manufacturers to comply with prequalification requirements. Current strategies for improving compliance include increased communication with manufacturers — with a focus on the benefits for manufacturers of prequalification — and rapid provision of feedback concerning the quality of their products after dossier submission.

Three inspections of API manufacturers were carried out, in cooperation with the Division of the Certification of Substances, of the European Directorate for the Quality of Medicines (EDQM), of the Council of Europe.
The results — positive or negative — of dossier assessments and inspections are communicated carefully to manufacturers and CROs. This technical feedback (which is provided free of charge) has proved to be of great practical value because it helps manufacturers and CROs to improve the quality of their products and their clinical studies.

Prequalification of NPQCLs follows similar procedures. An NPQCL must respond to an Expression of Interest and submit a laboratory information file for assessment. If the file is approved, the laboratory is then inspected to verify that its quality control activities are adequately rigorous for monitoring medicines quality. NPQCLs are not only inspected but also assisted to reach prequalification status through provision of customized technical guidance and assistance — in the form of inventory audits — to improve laboratory management and practice. NPQCLs are vital to ongoing quality control of prequalified products. That is, they check the quality of medicines circulating on the market. In the case of medicines that have previously been prequalified, they check that the prequalified medicines continue to comply with internationally determined and agreed standards for pharmaceutical safety, efficacy and quality.

**PREQUALIFICATION OF PRODUCTS FOR MALARIA**

During the nine dossier assessment sessions, 73 assessment reports were written, linked to more than 40 malaria products. An ad hoc team of expert assessors was set up to assess malaria product dossiers during and outside regular sessions, and has been operational since the second half of 2005. However, only four new malaria product dossiers were submitted in 2005, reflecting continuing difficulties in this sector regarding provision of data. (Providing data on malaria products is difficult owing to the lack of suitable ICH-approved comparators.) One of the 2005 Copenhagen sessions was specifically aimed at addressing the safety and efficacy elements of submitted malaria product dossiers. Six GMP manufacturing-site inspections and two API manufacturing-site inspections were conducted.

**Progress on artemisinin-based antimalarials**

In September, WHO experts met to review the current guidelines for prequalifying artemisinin-based antimalarials. The objective was to find means of encouraging and enabling greater numbers of manufacturers to submit their products for prequalification, and to meet prequalification requirements.

The meeting recommended:

- preparation of a preclinical pharmacology-toxicology summary of artemisinin derivatives to help applicants in preparing their dossier submissions — a draft was prepared and has since been finalized
- preparation of a model summary of product characteristics (SPC) for artesunate, also to guide applicants in preparing their dossier submissions — a draft model is currently under review.

These materials will be posted on the prequalification web-site, to encourage manufacturers to improve the quality of dossier submissions for antimalarials.
The dossier assessments and inspections are carried out by a group of qualified, external experts from national medicines regulatory agencies (NMRAs), mostly from countries that are members of the Pharmaceutical Inspection Cooperation/Scheme. They provide assessment and inspection support to a core team at WHO headquarters.

The Programme actively seeks the participation of regulatory staff from less well resourced NMRAs in Africa, Asia, Latin America, and the countries of central and eastern Europe, in dossier assessment sessions and inspections. Such participation constitutes valuable “on-the-job” training. Additionally, workshops are organized for regulatory staff (including NPQCL staff) and manufacturers to alert them to common problems identified during the manufacture and development of generic medicines for HIV/AIDS, TB, malaria. By these means, valuable knowledge on medicines quality, efficacy and safety issues is transmitted. As a result, the capacity of manufacturers to produce good-quality generic products is increasing, as is the capacity of NMRAs and NPQCLs to monitor pharmaceutical quality.

Full details of the prequalification procedures and prequalified products can be found at: http://mednet3.who.int/prequal/

PREQUALIFICATION OF NPQCLs
NPQCLs started to be prequalified in 2005. Three NPQCLs were prequalified — 2 university-based laboratories in South Africa and a laboratory in Algeria. All are listed on the prequalification web-site.

By the end of 2005, more than 15 laboratories had expressed interest in gaining approval; and 13 of them had submitted a laboratory information file, the first stage of the process. The files were evaluated and five inventory audits (as a means of guiding NPQCLs on needed improvements to laboratory practice and management) were carried out.

ACTIVITIES COVERING ALL PRODUCT GROUPS

Guidance on comparator products
A special document to guide manufacturers in the selection of suitable comparator products for bioequivalence studies was written by experts and published on the prequalification website — Note to applicants on the choice of comparator products for the Prequalification Programme. It includes lists of suitable comparators for HIV/AIDS, malaria and TB medicines. The Note will serve as an interim solution until finalization of the revision of Annex 11 of Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multi-source (generic) products (published as Technical Report Series, No. 902, 2002) and its publication.

TRAINING AND HANDS-ON PRACTICE
Recognizing the importance of capacity building through training and hands-on practice, the prequalification team organized six workshops on prequalification issues. Participants included local and international medicines manufacturers, local and international medicines regulators, and experts and inspectors involved in dossier assessment, clinical studies, bioequivalence and quality assurance. Most workshops included group sessions with task work. Communication between manufacturers and inspectors was open and collegial, and promoted mutual understanding concerning quality problems. Feedback on the workshops has been very positive: they are seen as a catalyst for increasing capacity to ensure medicines quality. Workshop details are given below.
**WHO BENEFITS FROM PREQUALIFICATION?**

**People at risk from and/or infected with HIV/AIDS, TB and/or malaria:** For HIV/AIDS patients, in particular, scaled-up access to medicines of assured quality is leading to a vastly improved quality of life. It is also helping to reduce wasted expenditure on substandard medicines, be this at household level for medicines purchased by individuals and their families, at national level for medicines purchased by central medical stores, or at the level of global treatment initiatives. In other words, more patients are being treated optimally.

**National medicines regulatory authorities (NMRA):** In resource-limited settings, in particular, the Prequalification Programme is helping medicines regulatory staff to increase their technical capacity to monitor and ensure the quality of medicines, particularly those for treating HIV/AIDS, TB and malaria. This includes developing greater understanding of: dossier assessment for new generic medicines; good manufacturing practice (GMP) adherence and GMP inspection; and how to overcome problems resulting from poor manufacturing practices. For NMRA Programme participants from developed countries, the principal benefit is a greater understanding of regulatory problems in resource-poor settings and problems encountered by pharmaceutical manufacturers outside their jurisdictions.

**Workshop 1:** Malaysia  
February (5 days)  
*Subject:* Dossier requirements for TB products (pharmaceutical quality, bioequivalence and GMP).

**Workshop 2:** China  
February/March (5 days)  
*Subject:* Dossier requirements for HIV products (pharmaceutical quality, bioequivalence and GMP).

**Workshop 3:** South Africa  
April and June/July (2 x 5 days)  
*Subject:* GMP for inspectors of South Africa’s Medicines Regulatory Authority.

**Workshop 4:** China  
May (9 days)  
*Subject:* GMP for inspectors of the State Food and Drug Administration of the Jiangsu and Zhejiang Provinces.

**Workshop 5:** Ukraine  
October (5 days)  
*Subject:* Dossier requirements for HIV and TB products (pharmaceutical quality, bioequivalence and GMP).

**Workshop 6:** Tanzania  
October (5 days)  
*Subject:* GMP for inspectors of Tanzania’s Food and Drug Authority.

**Training materials initiative**

The Technical Office for Studies on International Cooperation (Office Technique d’Etudes de Coopération Internationales, OTECI) agreed to translate training material on GMP into French (for completion in 2006). The translated material will be a major contribution to training workshops to be held in francophone Africa.

**ADVOCACY AND AWARENESS**

Prequalification team members took part in more than 10 meetings in 2005. By presenting and explaining the Programme’s activities they helped to maintain awareness and understanding of the need for and impact of prequalified medicines. The meetings included:

- The annual meeting of WHO Medicines National Professional Officers (NPOs), in Nairobi, in February, which was attended by Africa-based NPOs, as well as some of their Ministry of Health counterparts.
National pharmaceutical quality control laboratories (NPQCLs): For functional developing country NPQCLs, benefits include increased capacity to assess the quality of medicines samples, not simply for medicines for treating HIV/AIDS, TB and malaria, but medicines in general.

Pharmaceutical manufacturers in developing countries: The capacity of this very diverse group to produce medicines of assured quality, efficacy and safety is being enhanced, in turn reducing reliance on imports, and increasing opportunities for export. Manufacturers have already been assisted in improving the quality of their dossier submission. An increased number of generic medicines manufacturers now routinely submit dossiers that include sufficient detail regarding proof of safety, efficacy and quality. In short, the Programme offers manufacturers a tremendous opportunity to obtain technical guidance free of charge, that is of the highest calibre and that might otherwise be unavailable to them.

National disease control programmes and global health initiatives: Prequalification not only reduces the risk of expenditure on poor-quality, ineffective or counterfeit medicines, but is also extending the range of suppliers of good-quality medicines. Given extension of treatment to unprecedented levels, this is critical.

- The annual Technical Briefing Seminar on Essential Medicines Policies, in September, in Geneva, for a selected group of 35 core nationals representing ministries of health, regulatory agencies, professional pharmaceutical associations and nongovernmental organizations (NGOs), as well as WHO field staff.
- The annual meeting organized by AFSSAPS, in Paris, in November, on public health problems (especially those related to HIV/AIDS) faced by sub-Saharan French-speaking African countries.
- Roundtable (Mieux s’engager dans la lutte contre le sida, le paludisme et la tuberculose) organized by ReMed (Réseau Médicaments et Développement), a French NGO, in Paris, in November.
- The Center for Drug Evaluation and Research Forum for International Drug Regulatory Authorities held at US FDA offices in Rockville, USA, in September. Discussions took place on collaboration between the Prequalification Programme and the US FDA, and on the FDA’s tentative approval process for generic ARVs.

Additionally, Programme staff briefed national and international journalists on medicines quality issues, helping to maintain public awareness of the need not only to increase access to essential medicines but also to improve medicines quality globally.

TRANSPARENCY ABOUT MEDICINES QUALITY

The Programme includes a focus on transparency, especially regarding quality issues relating to generic medicines. Information collected and results obtained during assessments and inspections are (subject to confidentiality requirements) made publicly available through WHO prequalification web-pages and published reports.

WHO Public Assessment and Inspection Reports are a major means of communication. (In 2004, the World Health Assembly requested that WHO’s prequalification activities be made more transparent, including making assessment reports and inspection reports publicly available.) The prequalification team has created a standardized format for the WHO Public Assessment Report (WHOPAR). WHOPARs are posted on the prequalification website. The
Access to ARV therapy is set to expand ten-fold by 2010, based on the commitment made by the Group of Eight in 2005, and current funding commitments for treatment of malaria with artemisinin-based combination treatment is driving a one hundred-fold increase. Without quality medicine supplies, these increases will be impossible.

VALUE FOR MONEY

The Prequalification Programme is helping to ensure that donor funds are spent on good-quality medicines and achieve maximum impact. Indeed, the Global Fund to Fight AIDS, TB and Malaria (GFATM) now stipulates that any single- or limited-source pharmaceuticals procured with GFATM funds must have been prequalified by WHO. Prequalification of products in turn puts pressure on manufacturers to bring prices down, which also serves to optimize use of donor resources.

web-site includes guidance for manufacturers regarding these reports and information on how the reports are compiled by the prequalification team. (When submitting a product dossier for assessment, manufacturers must include specified documentation for inclusion in the WHOPAR that will later be compiled on their product.)

A standardized format was also developed for WHO Public Inspection Reports (WHOPIRs), which summarizes the technical issues covered by an inspection. Completed WHOPIRs are posted on the prequalification web-site and serve as useful reference material for anyone interested in the medicines prequalification process.

NEW COLLABORATION

Copenhagen HIV Programme

In 2005 the prequalification team launched a new collaboration with the Copenhagen HIV Programme (CHIP), based in Denmark’s Hvidovre University Hospital. The CHIP collaboration will promote consistency of clinical information about ARV products, as well as help to reduce the timeline for provision of acceptable and useful SPCs. Activities will focus on reviewing safety and efficacy information relating to ARV products and contained in WHOPARs. Under the collaboration, a standardized text on safety and efficacy for APIs and API combinations has already been drawn up, to be used as a basis for developing SPC texts.

The ultimate goal is generation of up-to-date medical information about prequalified ARVs, to be included with the products, to help ensure their appropriate and effective use.

US FDA and other regulatory authorities

A number of HIV products approved or tentatively approved by the US FDA were recently added to the list of products prequalified by WHO. These additions relied on the scientific assessment and inspections already conducted by the US FDA. Relevant information was exchanged, in accordance with a confidentiality agreement signed by the two organizations in 2005.

Collaboration is also being developed with the European Commission and European Medicines Evaluation Agency. In December, the Prequalification Programme was invited to participate in the GCP6 Inspection Services Group Meeting. The aim was to explore more effective...
The expansion of ARV therapy in Africa provides ample illustration of the health impact resulting from the financial savings generated by the Programme. Between June 2004 and June 2005, coverage increased by 350,000 people, to half a million people living with HIV. Most were enrolled to one of WHO’s recommended first-line regimens. On average, these regimens are available for US$ 560 per patient per year when purchased from innovator companies. Generic companies, whose products have been widely available only as a result of WHO prequalification (and whose availability accords with national law and donor policy), provide these regimens for less than US$ 190 per patient per year. Assuming that 80% of those enrolled in Africa in the last year began treatment with these regimens, the value of using prequalified generic products can be quantified as more than US$ 100 million. (This is the difference in total cost of using these medicines rather than comparable innovator products for 280,000 patient-years.) This sum, when reinvested, provides an additional 560,000 patients with access to one year of treatment.

ways of sharing and exchanging inspection-related information, in order to benefit from each other’s work and to avoid duplication.

A confidentiality agreement similar to the one with the US FDA is being developed to facilitate cooperation between the Prequalification Programme and Health Canada’s Health Products and Food Branch.

PUBLICATIONS AND INFORMATION

The prequalification website (http://mednet3.who.int/prequal/) was updated frequently in 2005. Newly prequalified products and NPQCLs were posted, as were new or revised guidance documents, together with WHOPARs, WHOPARs and workshop training materials.

During 2005, 11 WHOPARs for specific products and 15 WHOPARs covering all types of inspections, were posted. More than 10 additional WHOPARs will be published in early 2006 for other products prequalified in 2005.

The Prequalification Programme also published the three articles listed below. The first two articles describe general prequalification principles and procedures, while the third outlines ongoing quality monitoring of antiretroviral medicines.


Guidance documents

Revised versions of three guidance documents were posted on the prequalification web-site:

- *Guidance on submission of documentation for prequalification of innovator finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis and approved by drug regulatory authorities (DRAs) in the International Conference of Harmonisation (ICH) region and associated countries, including among others the EU, Japan and USA*
MILLENNIUM DEVELOPMENT GOALS

Each of the impacts described above is contributing to achieving the following targets set under the Millennium Development Goals:

- **Target 7**: to have halted by 2015 and begun to reverse the spread of HIV/AIDS
- **Target 8**: to have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
- **Target 17**: in cooperation with pharmaceutical companies, provide access to affordable, essential drugs in developing countries.

WHO’s prequalification activities are clearly a critical step in the pathway to expanding access to priority medicines. As The Lancet comments: “...prequalification status means that some of the most important drugs are being made safely available in parts of the world where they are most needed.”

New guidance documents were also posted on the web-site:

- **Guideline on submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis**
- **Note to applicants expressing interest for supplying artemisinin-containing drug products: bioequivalence, or efficacy and safety issues.**

Several guidance documents were translated into French:

- **Good practices for national pharmaceutical control laboratories**
- **Guidelines for preparing a laboratory information file**
- **Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies.**

Several Invitations for Expression of Interest were posted on the Prequalification Programme’s web-site:

- **6th Invitation for Expression of Interest (EOI): HIV and related diseases — October 2005.**
- **6th Invitation for Expression of interest (EOI): Antituberculosis — May 2005.**
- **4th Invitation for Expression of Interest (EOI): Artemisinin-based antimalarial products — May 2005.**

INFORMATION MANAGEMENT

A database was developed in 2005 to log and track dossier assessment, inspections, etc. It also incorporates all correspondence with manufacturers, as well as assessment and inspection reports.