WHO PREQUALIFICATION OF MEDICINES
PROGRAMME UPDATE FOR 2006

VITAL TO HEALTH GOALS

Imagine carrying your weak and feverish child to the nearest health clinic. Imagine the doctor making his diagnosis and prescribing an expensive antimalarial drug. Believing 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.

Expanding the list of prequalified medicines, together with capacity building in developing countries, remained the principal objectives in 2006. Forty-four products were added to the list, representing an increase of 38% over 2005, when 32 products were prequalified. Thirty-one of the 44 products were generic products. As in 2005, more generic than brand-name medicines were prequalified, illustrating the continued success of the Programme in capacity building in the generic sector.

DOSSIER ASSESSMENTS

The Programme was pleased to observe the continuing improvement in the quality of product dossiers submitted for assessment. However, this trend does not apply equally across all product areas and technical issues. Technical guidance and assistance to manufacturers will thus need to be maintained.

Six assessment sessions were organized at the UNICEF Supply Division in Copenhagen, where the product dossiers are received and stored. Four of the sessions were of five days duration and two of the sessions of nine days duration. During 2006, measures were taken to ensure a more continuous and efficient assessment process. The increased need for in-house assessment capacity was addressed. A professional assessor was seconded to the prequalification team at WHO Headquarters and a rotational post was created whereby a developing country assessor spends three months working with the in-house team. Additionally, individual assessors who remained at their home institution and location assisted the Programme by carrying out specific tasks. These included assessing variation applications in between planned sessions.
The Programme was launched in 2001, in partnership with UNAIDS, UNICEF and the UN Population Fund, with support from the World Bank. Its focus was tackling the quality problems commonly associated with medicines for treating HIV/AIDS, malaria and tuberculosis (TB).

Quality problems with medicines for treating HIV/AIDS, malaria and TB

- **HIV/AIDS**: For people living with HIV/AIDS, antiretroviral 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.

- **TB**: Many generic anti-TB medicines have serious quality defects, due to their poor manufacturing quality. Also, bioequivalence has often not been proved.

Product dossiers relating to products for treating HIV/AIDS, malaria and tuberculosis (TB) products were examined in each session and also between sessions. A total of 496 assessment reports (linked to 435 different products) were written during the six assessment sessions, representing a 45% increase over the number of reports (342) written during 2005.

**INSPECTIONS**

Forty-nine inspections were carried out (compared with 52 in 2005, when the inspection capacity of the Programme was slightly higher), as follows:

- 17 inspections (compared with 20 in 2005) of the manufacturing sites of finished product manufacturers
- 10 inspections (the same number as in 2005) of the manufacturing sites of active pharmaceutical ingredients (APIs)
- 15 inspections (compared with 14 in 2005) of contract research organizations (CROs)
- 7 inspections (compared with 8 in 2005) of quality control laboratories (QCLs), mostly in Africa.

An overview of inspections performed, listing manufacturing sites, CROs and QCLs that comply with WHO norms and standards regarding good manufacturing practice (GMP), good clinical practice (GCP) and good laboratory practice (GCP), respectively, continues to be maintained on the prequalification web-site (http://www.who.int/prequal/).

<table>
<thead>
<tr>
<th>Table 1: Details of dossier assessments carried out in 2006</th>
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<tbody>
<tr>
<td>Number of assessment sessions in Copenhagen</td>
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<tr>
<td>Number of assessment days</td>
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<tr>
<td>Total number of assessment reports produced</td>
</tr>
<tr>
<td>Number of assessment reports produced on HIV/AIDS products</td>
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<tr>
<td>Number of assessment reports produced on TB products</td>
</tr>
<tr>
<td>Number of assessments produced on malaria products</td>
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Then in 2006, the Programme laid the groundwork for prequalifying medicines and commodities for reproductive health. This was in response to the fact that, in many developing countries, the need for family planning and reproductive health services remains urgent. For example, 130 million couples wishing to use modern contraception do not have access to family planning services, and 340 million new cases of treatable sexually transmitted infections occur each year. Moreover, provision of reproductive health is often hampered by lack of reliable and good-quality supplies of medicines and commodities. And international donor support for reproductive health supplies is decreasing as a percentage of need and of use. As a result, reproductive health medicines and commodities are increasingly being funded and purchased by national governments. But they do not always have the necessary regulatory and procurement capacity for ensuring safe, effective and adequate supplies.

Considerable assistance with inspections was received from PIC/S member countries. WHO is hoping to encourage an increased number of PIC/S member countries to work with the Programme. France provided significant inspection support. Its own national medicines regulatory agency (NMRA) (Agence française de Sécurité sanitaire des Produits de Santé (AFSSAPS)) has individual inspection units for finished product, CRO and API inspections and so can make inspectors readily available for the finished product, CRO and API inspections conducted by the Programme. (France is one of the relatively few countries with significant CRO inspection expertise.) In 2006, the French Ministry of Health, AFSSAPS and WHO concluded an agreement whereby France provides technical support for the Programme’s inspection activities.

Of the inspections carried out in developing countries, 90% included participation not only of PIC/S inspectors, but also of up to three local inspectors.
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 (EOI), 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 consulted. When the dossier is close to approval, inspection of the manufacturing site(s) (of the active pharmaceutical ingredient and the finished product) is organized.

PREQUALIFICATION OF PRODUCTS FOR HIV/AIDS

Forty-two antiretroviral (ARV) products were prequalified (29 of which were generics), bringing the number of HIV-related products on the list of prequalified products to 154. Of the 42 products, 17 had been approved or tentatively approved by the US Food and Drug Administration (US FDA), and one product had been tentatively approved by Health Canada.

During the six dossier assessment sessions, 389 assessment reports, linked to 334 HIV/AIDS-related products were written, representing an increase of 75% over the figure for 2005. Twelve GMP inspections were carried out for HIV/AIDS medicines, including three three-year re-inspections and six inspections for ARV APIs. Eight inspections of CROs were conducted, corresponding to 10 bioequivalence studies of HIV/AIDS medicines.
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.

The results — positive or negative — of dossier assessments and inspections are communicated 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 clinical studies.

Quality control of ARVs

“Post-approval” monitoring of the quality of prequalified products continued to be undertaken. (For an example, please see *Journal of Generic Medicines* article mentioned on page 11.) In 2006, the Programme participated in a large sampling/quality-control testing programme of ARV products, as well as in some smaller initiatives relating to investigation into safety and quality complaints regarding products that have not been prequalified.

PREQUALIFICATION OF PRODUCTS FOR TB

By the end of 2004, a total of eight TB products had been prequalified. However, no additional TB products were prequalified in 2005 or 2006. This was due to continued failure of manufacturers to comply with prequalification requirements. Strategies for improving compliance were maintained. These included increased communication with manufacturers, regarding, for example, the benefits of prequalification, and rapid provision of feedback concerning the quality of their products. Scientific advice, especially relating to bioequivalence and efficacy/safety was also provided to manufacturers. This advice included recommendations regarding clinical study design, choice of comparator products and review of submitted protocols.

Although no TB products were prequalified in 2006, the interest of TB manufacturers in prequalification of their products definitely grew. This interest was reflected in the 50% increase in the number of assessment reports that were produced: 78 assessment reports, linked to 70 TB products (as opposed to 50 assessment reports linked to around 50 products in 2005).

Ad hoc assessments of product dossiers continued to be undertaken by the Prequalification Programme as a service to the Global Drug Facility (GDF). These assessments consumed considerable resources (in terms of assessor and financial input). Since the GDF initiative has only partly achieved its objectives, these ad hoc assessments will be reviewed in 2007. Part of the problem stems from the fact that the available products are of relatively poor quality.
Eight GMP inspections were carried out for TB products, including two three-year re-inspections and three inspections of manufacturers of TB product APIs. Five inspections of CROs were conducted that corresponded to 11 bioequivalence studies for TB products.

Three of the inspections of API manufacturers were carried out in cooperation with the Inspection Programme of the Certification of Suitability Procedure, organized by the European Directorate for the Quality of Medicines of the Council of Europe.

PREQUALIFICATION OF PRODUCTS FOR MALARIA

During the six dossier assessment sessions in Copenhagen, 29 assessment reports, linked to 31 products were written (in comparison with 73 reports, linked to more than 40 malaria products in 2005). This drop in assessment reports was due to the drop in number of new submissions. It also reflected the slow progress made by manufacturers in addressing deficiencies identified by assessments carried out in 2005.

Several dossiers for malaria products were withdrawn by manufacturers, following revision of WHO treatment guidelines. The withdrawals concerned products that were not included in WHO’s new treatment guidelines for artemisinin-based combination therapies.4

Seven GMP inspections were carried out for malaria products, including one three-year inspection and one manufacturing site inspection. Two CRO inspections were conducted, corresponding to two bioequivalence studies of malaria products.

In common with the manufacturers of TB products, scientific advice relating to bioequivalence and efficacy/safety was provided to manufacturers of malaria products. This advice included recommendations regarding clinical study design, choice of comparator products and review of submitted protocols.

Additionally, a comprehensive summary of pre-clinical artemisinin toxicity (i.e. the results of experimental studies in animals and cell cultures) was posted on the Prequalification Programme web-site as an aid to manufacturers compiling
The dossier assessments and inspections are carried out by qualified, external experts from national medicines regulatory agencies (NMRAs), mostly from countries that are members of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S). They provide assessment and inspection support to a core team at WHO headquarters. (See also the reference to PIC/S on page 3.)

dossiers for artemisinin products. The Note to Applicants Expressing Interest in Supplying Artemisinin Containing Drug Products: Bioequivalence, or Safety and Efficacy Issues was revised accordingly.

Five antimalarials are now included on the list of prequalified products.

PREQUALIFICATION OF REPRODUCTIVE HEALTH PRODUCTS

The first Expression of Interest (EOI) for reproductive health products was published on the Programme web-site in October 2006. Additional advice to manufacturers on how to compile a dossier for a reproductive health product, for example, on choice of comparator products, was also posted on the prequalification web-site.

PREQUALIFICATION OF QCLs

QCLs started to be prequalified in 2005, when three QCLs were prequalified — two university-based QCLs in South Africa and a national pharmaceutical QCL in Algeria. All are listed on the prequalification web-site.

Table 5: Summary of Prequalification Programme activities, and products prequalified, for 2005 and 2006

<table>
<thead>
<tr>
<th>Prequalification Programme activities and products prequalified</th>
<th>Number in 2005</th>
<th>Number in 2006</th>
<th>Percentage increase or decrease between 2005 and 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dossier assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment sessions in Copenhagen</td>
<td>9</td>
<td>6</td>
<td>−33.3</td>
</tr>
<tr>
<td>Number of assessment days</td>
<td>45</td>
<td>42</td>
<td>−6.6</td>
</tr>
<tr>
<td>Total number of assessment reports</td>
<td>342</td>
<td>496</td>
<td>+45</td>
</tr>
<tr>
<td>Number of assessment reports on HIV/AIDS-related products</td>
<td>222</td>
<td>389</td>
<td>+75</td>
</tr>
<tr>
<td>Number of assessment reports on TB products</td>
<td>50</td>
<td>78</td>
<td>+56</td>
</tr>
<tr>
<td>Number of assessment reports on malaria products</td>
<td>70</td>
<td>29</td>
<td>−59.6</td>
</tr>
<tr>
<td><strong>Inspections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspections of manufacturing sites of finished product manufacturers</td>
<td>52</td>
<td>49</td>
<td>−5.7</td>
</tr>
<tr>
<td>Inspections of manufacturing sites of active pharmaceutical ingredients</td>
<td>10</td>
<td>10</td>
<td>No change</td>
</tr>
<tr>
<td>Inspections of contract research organizations</td>
<td>14</td>
<td>15</td>
<td>+7.1</td>
</tr>
<tr>
<td>Inspections of national pharmaceutical quality control laboratories (QCLs)</td>
<td>8</td>
<td>7</td>
<td>−12.5</td>
</tr>
<tr>
<td><strong>Products, laboratories prequalified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of products prequalified</td>
<td>32</td>
<td>44</td>
<td>+38</td>
</tr>
<tr>
<td>Number of HIV/AIDS products prequalified</td>
<td>29</td>
<td>42</td>
<td>+44.8</td>
</tr>
<tr>
<td>Number of TB products prequalified</td>
<td>0</td>
<td>0</td>
<td>No change</td>
</tr>
<tr>
<td>Number of malaria products prequalified</td>
<td>1</td>
<td>2</td>
<td>+100</td>
</tr>
<tr>
<td>Number of QCLs prequalified</td>
<td>3</td>
<td>0</td>
<td>−100</td>
</tr>
</tbody>
</table>
By the end of 2006, 18 laboratories had expressed interest in gaining approval; and 15 of them had submitted a Laboratory Information File, the first stage of the process. Five pre-audit inspections of national pharmaceutical QCLs were carried out — all in Africa — as a means of providing guidance on improvements needed in laboratory practice and management.

Progress in prequalifying additional QCLs has been slow. The laboratories prequalified in 2005 were already operating at or close to the levels required for prequalification. But it has become clear that those laboratories now seeking prequalification status will require considerable technical assistance from the Programme, and must commit to making substantial operational improvements themselves. Technical assistance has been delivered to several national QCLs, including to laboratories in Ethiopia and Tanzania.

TRAINING WORKSHOPS ON PREQUALIFICATION ISSUES

Recognizing the importance of capacity building through training and hands-on practice, the prequalification team organized several training workshops on prequalification issues during 2006. These workshops provided tuition on general or specific technical issues for larger groups, including staff from NMRAs and QCLs, and from manufacturers or other private companies. (All workshop materials can be found on the prequalification web-site at http://www.who.int/prequal/.)

Such workshops include group sessions with task work. Efforts are made to ensure open and collegial communication between manufacturers and the presenters, who themselves are assessors or inspectors working with the Prequalification Programme. The overall aim is to promote mutual understanding concerning quality and efficacy/safety issues. Feedback on the workshops held to date has been very positive: they are seen as a catalyst for increasing capacity to ensure medicines quality. Four workshops were held in 2006, as follows:

Workshop 1: Guilin, China
January (5 days)
Subject: Pharmaceutical quality, GMP and bioequivalence, with a focus on artemisinines.
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.

Workshop 2: Hanoi, Viet Nam
January (3 days)
Subject: Pharmaceutical quality and bioequivalence.

Workshop 3: Paris, France
March (2 days)
Subject: GCP seminar for inspectors participating in the WHO Prequalification Programme.

Workshop 4: Dar-es-Salam, United Republic of Tanzania
August (5 days)
Subject: Pharmaceutical quality, GMP and bioequivalence, with a focus on artemisinines.

TRANSPARENCY ABOUT MEDICINES QUALITY

The Programme pays particular attention to increasing transparency around 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.) A standardized format is used for producing WHO Public Assessment Reports (WHOPARs). WHOPARs are posted on the prequalification website (with priority being given to fixed-dose combination products). The 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 is also used for WHO Public Inspection Reports (WHOPIRs), which are likewise posted on the prequalification web-site.

During 2006, 11 WHOPARs for specific products and 24 WHOPIRs, covering all types of inspections, were produced.
**NMRA**s: 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.

**QCLs**: For functional developing country QCLs, 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.

**UPDATE ON EXISTING COLLABORATION**

**Copenhagen HIV Programme**

The collaboration initiated in 2005 with the Copenhagen HIV Programme (CHIP), based in Denmark’s Hvidovre University Hospital, continues. Activities focus on reviewing safety and efficacy information relating to ARV products and contained in WHOPARs. Standardized texts on safety and efficacy for APIs and API combinations are developed and published, together with the corresponding WHOPAR, for prequalified products. The collaboration is helping to promote consistency of clinical information about ARV products, as well as to reduce the timeline for provision of acceptable and useful summaries of product characteristics.

**US FDA and other regulatory authorities**

A number of HIV products approved or tentatively approved by the US FDA were added to the list of products prequalified by WHO. These additions relied on the scientific assessment and inspections conducted by the US FDA. Information exchange between the two organizations is in accordance with a confidentiality agreement that was finalized in 2005.

Collaboration also continues to be developed with the European Commission and the European Medicines Evaluation Agency, particularly on sharing and exchanging inspection-related information.
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.

PUBLICATIONS AND INFORMATION


The prequalification website (http://www.who.int/prequal/) was updated frequently in 2006. Newly prequalified products and details of QCLs meeting prequalification requirements were posted, as were new or revised guidance documents, together with WHOPIRs, WHOPARs and workshop training materials.

A new and more user-friendly prequalification website was launched in November 2006.

Guidance

A new and revised guidance on variations (“changes”) to a prequalified dossier was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The guidance stipulates, among other things, that if manufacturers have notified the Programme of a variation or variations — belonging to a certain category as defined in the guidance — that they wish to make to a product, and are not contacted by the Programme within three months, then they may go ahead and implement those variations.

The EOI for reproductive health products was published on the Prequalification Programme web-site, as was a list of recommended comparator products within the area of reproductive health.

The lists of recommended comparator products for HIV/AIDS, TB and malaria products were revised and updated on an ongoing basis.

The following were adopted in October 2006 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations: Procedure for Assessing the Acceptability, in Principle, of Pharmaceutical Products for Purchase by United Nations Agencies (Annex 4) and Procedure for Assessing the Acceptability, in Principle, of Quality Control Laboratories for Use by United Nations Agencies.
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. Access to antiretroviral (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.

In due course, once medicines and commodities for reproductive health start to be prequalified, more individuals will be able to access family planning services and more individuals requiring treatment for sexually transmitted infections will be able to obtain such treatment.

Translation

The Technical Office for Studies on International Cooperation (Office Technique d’Etudes de Coopération Internationales — OTECI) completed translation of training material on GMP into French. It will be a major contribution to training workshops to be held in francophone Africa.

Translation into Chinese of the most important parts of the prequalification web-site started in 2006, in cooperation with the Chinese Ministry of Health.

INFORMATION MANAGEMENT

A database to log and track dossier assessment, inspections and other activities is being developed. It will also incorporate all correspondence with manufacturers, as well as assessment and inspection reports. The database is expected to become fully operational in 2007.

ADVOCACY AND AWARENESS

Prequalification team members took part in a variety of meetings in 2006, to present and explain the Programme’s activities. In so doing, they helped to maintain awareness and understanding of the need for and impact of prequalified medicines.

The most important meeting was that of the International Conference of Drug Regulatory Authorities (ICDRA). ICDRAs have been held every two years since 1980. They provide regulatory authorities of WHO Member States with a forum for discussing national and international priorities for regulation of medicines, vaccines, biomedicines and herbal medicines. They are key to efforts to harmonize regulation and to improve the safety, efficacy and quality of medicines globally.

(Annex 5). The first document is an update to the already existing general procedure for prequalifying medicines, while the second document describes general procedures for prequalifying QCLs. I.e. taken together, these documents describe the general principles of prequalification.
**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) 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 national and donor resources.

The 12th ICDRA, took place in 2006 in Seoul, Republic of Korea and was attended by regulators from nearly 100 countries. It included a session, “Access to medicines: new regulatory pathways for public health needs” that included presentations on: procedures relating to access to medicines under Article 58 of European Union legislation; the United States FDA’s tentative approval procedure linked to the President’s Emergency Plan for AIDS’s Relief (PEPFAR); the Canadian access to medicines regime; and the WHO Prequalification Programme. The following recommendations resulted from this session:

1. In the assessment of products, particularly those developed for public health needs, countries should make use of new regulatory pathways provided by highly-evolved regulatory agencies in order to avoid duplication of effort. This would enable optimal use of limited resources.

2. In cooperation with well-resourced regulatory agencies, WHO is urged to assist Member States to provide training on the best use of regulatory information on product approvals available in the public domain.

3. WHO should continue its efforts to prequalify APIs for priority diseases, including HIV/AIDS, malaria and TB. Information concerning prequalified products and approved sites should continue to be made public in the form of WHOPIRs.

4. WHO should assist national regulatory agencies to develop innovative approaches to improve access to safe and effective essential medicines of quality which address public health needs.

The proceedings of the 12th ICDRA, together with all power point presentations, are available on the WHO medicines web-site: http://www.who.int/medicines/icdra/en/
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.

Other meetings attended by Programme staff in 2006 included:

- 2nd Seminar on National Policy on Medicines, São Paulo, Brazil, in April.
- Meeting on artemisinin-based combination therapies organized by Drugs for Neglected Diseases Initiative and held in June, in Geneva, Switzerland.
- 42nd meeting on improving access to quality-assured TB drugs, organized by the Campaign for Access to Essential Medicines, of Médecins Sans Frontières (MSF), in Geneva, Switzerland, in June.
- Rencontre d’été (summer meeting) on paediatric medicines for treatment of HIV/AIDS, TB and malaria, organized by ReMed (Réseau de Médicaments et Développement), a French nongovernmental organization (NGO) in Paris, in July.
- 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 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 francophone African countries.
- Interagency Pharmaceuticals Coordination Group meeting at the Pan American Health Organization, in Washington, DC, in November.
- Interagency meeting on medicines issues organized by MSF in Paris in November for pharmacists working with NGOs or international organizations.
- World Trade Organization workshop on the TRIPS Agreement and public health, held in Geneva, in November.
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.

At a later stage, prequalification of reproductive health medicines and commodities will contribute not only to Targets 7 and 17, but also to an additional target:

- **Target 6**: to reduce by three-quarters, between 1990 and 2015 the maternal mortality ratio.

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.

TECHNICAL ASSISTANCE

Selection of independent experts for provision of technical assistance

Since its inception, the Programme has been working hard to build the capacity of both regulators and manufacturers. Additionally, in the latter half of 2006, it started to coordinate efforts to provide customized technical assistance aimed at resolving the specific technical problems of individual NMRAs, manufacturers or laboratories.

Distinguishing between capacity building and technical assistance

Within the Prequalification Programme, **capacity building** focuses on strengthening the capacity of regulatory authorities, pharmaceutical manufacturers and national QCLs to follow procedures for guaranteeing the quality and safety of medicines. **Technical assistance** is defined as customized assistance provided to a single regulatory authority, manufacturer or laboratory. In terms of manufacture, it addresses bottlenecks in the development and manufacture of good-quality products. As such, it focuses on specific products and specific problems relating to their production. Similarly, technical assistance to national QCLs focuses on specific problems that a laboratory must tackle if it is to comply with the Programme’s requirements for QCL prequalification.

Twenty experts — working either for nonprofit organizations such as OTECI, or acting as highly specialized technical, private consultants — can be called upon to provide technical assistance and support to regulators, manufacturers or laboratories. Whenever an expert visits a country, the NMRA is consulted and also given the opportunity to organize a general training workshop on quality and safety issues with the expert’s participation.

The activities of these experts are strictly independent of any Prequalification Programme assessment or inspection activities. In other words, involvement in technical assistance automatically excludes an expert from participation in any prequalification assessment or inspection activity.
In 2006, technical assistance was organized as follows:

**Technical assistance for manufacturers and regulators**

**Technical assistance: Tanzania**
October/November (13 days)
*Subject:* Good practices for QCLs, and analytical method validation and verification.

**Technical assistance: Ethiopia**
October (5 days) and November/December (10 days)
*Subject:* Good practices for national QCLs, and analytical method validation and verification.

**Technical assistance and customized training for manufacturers**

**Training: China**
June 2006 (2 days)
*Subject:* Pre-audit inspection of CROs and GCP.

**Training: Thailand**
August/September 2006 (5 days)
*Subject:* Requirements relating to quality section of dossiers.

**Training: Ukraine**
October 2006 (3 days)
*Subject:* Requirements relating to quality section of dossiers.

**Training: China**
October 2006 (5 days)
*Subject:* GMP compliance for aseptic preparation of injectable artesunate.

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1. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S) are mechanisms for promoting cooperation, among participating national inspectorates, in the area of GMP.
2. A comparator product is used to test the quality of both innovator products and their generic alternatives, and to ensure that two substances under investigation are chemically identical.
3. The Global Drug Facility is a mechanism aimed at expanding access to and availability of existing high-quality TB drugs to facilitate global expansion of DOTS, a public health strategy to control TB, which is currently available for only 27% of all TB patients.
5. Pre-audit inspections are offered to national laboratories, but not to commercial laboratories.
6. OTECI is a French nongovernmental organization. It enables retired professionals with experience in, for example, the health, agricultural or textile sectors, to contribute their expertise to development programmes.
7. Customized training and assistance was provided to two CROs (one of which focuses on clinical studies and the other on biomathetical studies), which were responsible for performing a bioequivalence study for a co-blistered formulation of artesunate and amodiaquine. The CROs received training on compliance with GCP and GLP.
8. Customized training and support on ensuring GMP compliance was given to a Chinese manufacturer of artesunate powder. However, inspection of the manufacturing site thereafter found that it still did not comply with current GMP requirements for sterile production. An independent expert was engaged to work with the manufacturer for one week to remedy observed problems.