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WHO Drug Information

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Quality of Medicines

WHO medicines prequalification: progress in 2008

The WHO Prequalification Programme for Medicines (PQP) was initiated in 2001 as a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified international standards of quality, safety and efficacy for HIV/AIDS, malaria, tuberculosis and reproductive health.

The work is carried out through:

- Stringent assessment of pharmaceutical product dossiers.
- Inspection of pharmaceutical manufacturing sites (both for finished dosage forms and active pharmaceutical ingredients) and contract research organizations (CROs).
- Prequalification of pharmaceutical quality control laboratories (QCLs).
- Advocacy for medicines of assured quality.

The Bill & Melinda Gates Foundation as well as UNITAID are the main financial supporters of PQP.

Newly prequalified medicines
Forty products were added to the list of prequalified medicines in 2008, an increase from 21 products in 2007. The total number of prequalified medicines currently stands at 196.

A major achievement in 2008 was the prequalification of new products specially designed to treat HIV/AIDS in children, as well as the first fixed-dose combination tablets of artesunate and amodiaquine to treat malaria. These products represent a considerable breakthrough in making user-friendly formulations available that will also improve efficacy of treatment.

The number of products prequalified in 2008 was the highest in six years. The main reasons for this were:

- Increasing number of well prepared new submissions in 2007–2008.
- Improved quality of evidence to demonstrate quality, safety and efficacy of products.
- Expanded staffing component in 2007.
- Implementation of management efficiency tools which improve the evaluation process.

List of prequalified medicines
Inclusion in the list does not mean that the prequalification status of a product is assured indefinitely. All approved medicines have to be checked regularly to ensure that any changes undertaken by manufacturers do not undermine the quality, safety and efficacy of the product.

In order to achieve this objective, WHO carries out re-inspections of manufacturing sites as well as random quality control tests of prequalified medicines. Since the prequalified products list is constantly being added to, information maintenance and updating becomes crucial to the preservation of established international standards.

New submissions to PQP
Certain product groups are urgently in need of expansion to increase available

In 2008, the WHO Medicines Prequalification Programme:

- Prequalified a total of 40 medicinal products. The list of prequalified medicines now contains nearly 200 products.
- Prequalified the first ever fixed-dose combination tablets of antiretroviral medicines designed for use in children to treat HIV/AIDS, and the first fixed-dose combination tablets of artesunate and amodiaquine to treat malaria.
- Organized 11 training workshops for capacity building in resource-limited countries for staff of regulatory authorities and pharmaceutical manufacturers.
- Provided manufacturers with scientific advice and technical assistance to support improvements in the quality of their products.
- Implemented the biowaiver concept to facilitate evaluation of product dossiers.
- Prequalified six quality control laboratories.
- Planned and implemented three comprehensive medicines sampling and testing programmes in countries that were recipients of drug donations.
- Revised and updated the procedure for prequalification to increase transparency and accountability of prequalification performance.
- Contributed to the development of guidelines and standards to facilitate global quality assurance activities, including pharmacopoeial monographs and chemical reference standards.
- Opened prequalification to include zinc and influenza products and considerably expanded the invitation list of reproductive health products.

treatment options (e.g., second-line antituberculosis and paediatric antiretroviral combination products). However, it was again noted that the number of products submitted for evaluation within this category was insufficient to meet current demand. This is mainly due to a lack of commercial incentives available to manufacturers to develop products intended for small or non-profitable markets.

In the past year, the number and quality of product dossiers submitted for assessment continued to present many challenges. Newcomer manufacturers having limited or no experience in production according to international standards have great difficulty in submitting the evidence required. Insufficient quality specifications presented for reproductive health and antimalarial products and manufacturing conditions are of particular concern.

In recent years, documented quality assurance of medicines has become an essential requirement of international funding agencies for successful bidding in procuring essential medicines for developing countries. Manufacturers should therefore be increasingly motivated to invest in enhancing their own manufacturing and control processes to improve the quality of submissions to the PQP.

Technical assistance to manufacturers

Time and resources are needed from applicants to obtain product prequalifica-

tion and this includes dedication to implementation of corrective action to meet international quality standards. It follows that an increase in the number of available prequalified medicines can only be achieved based on increased capacity building and technical assistance activities.

Consequently, since 2006, the PQP has provided coordinated technical assistance aimed at resolving specific practical problems encountered by manufacturers or quality control laboratories. Assistance is provided by qualified professionals in the form of an audit and training in technical or regulatory areas.

Such action in resource-limited countries has become one of the core activities of PQP since 2007 and will remain so for the following years. In 2008, PQP provided eight technical assistance missions to pharmaceutical manufacturers in five different countries.

Training
WHO recognizes the crucial role of capacity building through training and hands-on practice. In 2008, PQP organized 11 training courses and co-organized four training activities together with other partners in 10 different countries (see table on page 7).

This tuition on general or specific technical issues is also offered to larger groups formed by manufacturers, national medicines regulatory agency staff and professionals from quality control laboratories. Training courses include group sessions as well as focused communication between the involved parties, such as manufacturers and lecturers who are part of the assessment or inspection teams working with PQP. In 2008, these courses involved more than 600 participants and 46 lecturers and trainers provided by PQP.

Capacity building of regulatory authorities
In 2008, the PQP continued to offer national regulatory personnel from resource-limited countries a three-month full-time post at WHO. These rotational positions for quality assessors are aimed at creating links and form a network between WHO and the countries involved, as well as enhance information exchange between both parties.

In addition, assessors from less resourced regulatory authorities continue to participate in PQP assessment sessions where they account for one-third of the total external assessor contribution. Since 2008, inspectors from these authorities are invited to take part in WHO inspections as observers. Regulators from the WHO Africa Region have been especially active in this process.

Dossier assessments and expert advice
In 2008, seven assessment sessions were organized at the UNICEF Supply Division in Copenhagen where product dossiers are received and stored. The number of assessment reports for 2008 increased to 732 compared to 463 in 2007. In addition to regular assessment activities, provision of expert scientific advice to applicants remained high on the agenda. In 2008, a total of 13 bioequivalence study protocols were reviewed, more than 60 bioequivalence queries answered, and close to 80 separate quality issues handled by the respective expert panels.

Inspections
A total of 38 inspections of pharmaceutical manufacturers and 14 inspections of CROs were carried out in seven different countries in 2008. As in all previous years, the national inspectorates from well established regulatory authorities continued to provide staff inspectors for

Prequalification assessment and inspection statistics

	2007	2008
Dossier Assessment		
Assessment sessions in Copenhagen	6	7
Total number of assessment days	42	46
Total number of assessment reports	463	732
Assessment reports on HIV/AIDS products	298	494
Assessment reports on TB products	100	100
Assessment reports on malaria products	54	115
Assessment reports on reproductive health products	11	19
Assessment reports on influenza products	-	4
Inspections	46	62
Manufacturing sites of finished product manufacturers	26	27
Manufacturing sites of active pharmaceutical ingredients	6	11
Contract research organizations	13	14
Pharmaceutical quality control laboratories	1	10

prequalification purposes. France was the leading country in terms of providing inspection support.

Prequalification of quality control laboratories

The prequalification of quality control laboratories was restarted in 2007 when 12 laboratories expressed interest in prequalification. In 2008, PQP carried out 10 inspections of quality control laboratories with six gaining prequalification status.

Testing of medicines

The prequalification status of a medicinal product guarantees its quality at the time of delivery to the recipient country. However, quality can deteriorate during transportation and storage. To verify that the quality of essential medicines is maintained throughout the supply chain until the medicines reach the end user, several sampling and testing programmes have been designed and implemented.

Programme strengthening and development of standards

Major procedural improvements to PQP in 2008 include:

- Revision and update of the procedure for prequalification to increase transparency and accountability of PQP.

Major medicines testing programmes organized by WHO PQP in 2008

Aim of sampling and testing	Countries involved	Total number of samples
Quality survey of anti-malarial medicines	Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania	936
Quality monitoring of products funded by UNITAID	Kenya, Tanzania, Uganda, Zambia	378
Quality survey of anti-TB medicines in Eastern Europe	Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan	360

Training workshops organized by WHO PQP in 2008

Date	Location	Content of training
25–29 February	Brasilia, Brazil	New approaches to quality risk management in manufacture of medicines.
21–25 April	Lahore, Pakistan	Development of PQP submission dossiers.
28 April–1 May	Mumbai, India	Pharmaceutical development with a focus on paediatric formulations.
2–6 June	Dar-es-Salaam, United Republic of Tanzania	Evaluation of generic products focusing on bioequivalence and biowaiver data.
16–20 June	Amman, Jordan	Introduction to PQP and technical requirements.
16–20 June	Teheran, The Islamic Republic of Iran	Introduction to PQP and technical requirements.
23–27 June	Beijing, China	GMP for reproductive health products and dossier requirements.
8–11 July	Rabat, Morocco	GMP – air and water treatment systems
20–24 October	Jakarta, Indonesia	GMP for reproductive health products and dossier requirements.
3–7 November	Accra, Ghana	Regulatory requirements and data assessment of artemisinin-based fixed dose combination medicines.
1–5 December	Nanchang, China	GMP training for SFDA inspectors

- Opening of new tracks for the prequalification of zinc and influenza products.
- Implementation of the biowaiver concept to facilitate evaluation of product dossiers.
- Publication of the first "notices of concern" highlighting good manufacturing practice (GMP) violations observed during inspections.

PQP activities are based on scientifically sound and updated internationally accepted quality standards. In 2008, development and updating of new and existing WHO guidelines and standards continued to facilitate global quality assurance activities. Such guidance includes pharmacopoeial monographs and chemical reference standards. The procedure for prequalification of active pharmaceutical ingredients was approved by the WHO Expert Committee on Pharmaceutical Specifications for implementation in 2009.

Reference: The Medicines Prequalification Programme (PQP). http://www. who.int/prequal

Herbal and Traditional Medicines

WHO Congress on Traditional Medicine and the Beijing Declaration

Representatives of over 70 Member States attended the first WHO Congress on Traditional Medicine held on 7–9 November 2008 in Beijing, China. Satellite symposia were held to discuss related technical topics. Presentations were given by representatives of organizations such as the World Self-Medication Industry (WSMI), the World Federation of Acupuncture-Moxibustion Societies (WFAS), the International Pharmaceutical Federation (FIP), and the World Federation of Chiropractic (WFC). Almost 1500 people were present at the events.

Highlights of the Congress included adoption of the Beijing Declaration promoting the safe and effective use of traditional medicine and calling on WHO Member States and other stakeholders to take steps to integrate traditional medicine, complementary and alternative medicines (TM/CAM) into national health systems.

Sharing of national experience and information by Member States in five areas aimed at leveraging future action.

- National policy on TM/CAM.
- National regulation of traditional and herbal medicines.
- TM use in Primary Health Care.
- National regulation of TM/CAM practice.
- Research on TM/CAM.

Participants visited community health centres, clinics and hospitals for traditional medicine. These models showed how traditional and Western medicine can work together and be successfully integrated into China's health system.

In 2008, WHO marked its 60th anniversary and the 30th anniversary of the Alma Ata Declaration, adopted by UNICEF and WHO in 1978. Although traditional medicine has been used for thousands of years and has made a fundamental contribution to human health, the Alma Ata Declaration was the first formal recognition of the role of traditional medicine and its practitioners in primary health care by WHO and its Member States.

Use of traditional medicine has changed dramatically over the past thirty years. Due to its affordability, availability and accessibility, traditional medicine has played an important role in meeting the demands of primary health care in many developing countries.

Since the 1990s, the use of traditional medicine has surged. It not only maintains its function in primary health care in developing countries (70–80% of the population in Ethiopia and India still depend on traditional medicine and practitioners for primary health care), its use has expanded widely in many developed countries where it is referred to as complementary or alternative medicine (CAM). For instance, 70% of the population in Canada and 80% in Germany have used CAM. National health authorities were asked to consider how to integrate TM/CAM into their national health systems and significant progress has been made since initiation of the WHO Traditional Medicine Strategy in 2002.

WHO Congress on Traditional Medicine

To further assess the role of traditional medicine/CAM, review the progress of the countries and help Member States integrate traditional medicine/CAM into their national health systems, the first WHO Congress on Traditional Medicine on 7–9 November 2008, was organized in Beijing, China. The Congress was hosted by the Ministry of Health and the State Administration of Traditional Chinese Medicine of the Government of China, in cooperation with four nongovernmental organizations (NGOs) in official relations with WHO — the World Self-Medication Industry (WSMI), the World Federation of Acupuncture-Moxibustion Societies (WFAS), the International Pharmaceutical Federation (FIP), and the World Federation of Chiropractic (WFC).

During the opening ceremony, the Director-General of WHO identified the importance of traditional medicine in primary health care, the role of research, the need for appropriate licensing or registration of practitioners and the importance of patient-practitioner interaction. It was noted that within the context of primary health care, the two systems of traditional and western medicine can blend together in beneficial harmony, using the best features of each system.

Delegates were welcomed by the Minister of Health, People's Republic of China. In their presentations, the Minister of Health of the Union of Myanmar and the Deputy Minister of Health of South Africa explored the role of integration of traditional medicine into primary health care and actions that their respective countries have taken. The need for appropriate regulatory oversight of complementary medicine products was expressed by the National Manager of the Therapeutic Goods Administration of Australia.

During the International Forum on Integration of Traditional Medicine/CAM into Health Systems, 26 delegates presented short national reports outlining the regulatory framework for traditional medicine, products and practice in their respective countries. To facilitate discussion, the presentations were separated into five topic areas:

- National Policy on TM/CAM and integration into national health systems.
- National regulation of traditional and herbal medicines.
- Traditional medicine in primary health care.
- National regulation of traditional medicine/CAM practice.
- Research and development of traditional medicine.

While presentations showed that it is often necessary to tailor legislation and delivery to reflect the needs and traditions of individual countries, a number of common themes and issues did emerge. Most notable of these were the importance of practitioner training, issues related to safety, need to enhance re-

search into both products and practices, importance of labelling and information as it relates to supporting informed choice, and the need for appropriate integration into primary health care.

Delegates also heard from two WHO partners (The Nippon Foundation and the Regional Government of Lombardy) who described their work in this area. The four nongovernmental organizations hosting satellite conferences were also given the opportunity to make presentations and observe the Congress.

A key outcome of the Congress was the Beijing Declaration, which identified common aims and principles reached by participants at the Congress. Preparation of the declaration was structured, starting some months prior to the Congress with circulation of the first draft. Comments were collected and modifications made with a subsequent draft sent to participants before the Congress. During the Congress, an *ad hoc* drafting team was created to discuss and harmonize the comments submitted to WHO prior to the Congress and to enable the Declaration to be presented to the Congress.

Congress delegates adopted the Beijing Declaration during the WHO Congress on Traditional Medicine. In addition to a preamble text noting a number of related initiatives and reflecting the importance of national contexts with regard to capacity, priorities and relevant legislation, the Beijing Declaration is set out below.

The Beijing Declaration will serve to promote the safe and effective use of traditional medicine, and calls on WHO Member States and other stakeholders to take steps to integrate traditional medicine/CAM into national health systems. During the closing of the International Forum the WHO Assistant Director-General for Health Systems and Services said, "This is a landmark declaration, after a landmark Congress."

Beijing Declaration

Adopted by the WHO Congress on Traditional Medicine, Beijing, China, 8 November 2008

Participants at the World Health Organization Congress on Traditional Medicine, meeting in Beijing this eighth day of November in the year two thousand and eight:

Recalling the International Conference on Primary Health Care at Alma Ata thirty years ago and noting that people have the right and duty to participate individually and collectively in the planning and implementation of their health care, which may include access to traditional medicine.

Recalling World Health Assembly resolutions promoting traditional medicine, including WHA56.31 on Traditional Medicine of May 2003.

Noting that the term "traditional medicine" covers a wide variety of therapies and practices which may vary greatly from country to country and from region to region, and that traditional medicine may also be referred to as alternative or complementary medicine.

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Beijing Declaration *(continued)*

Recognizing traditional medicine as one of the resources of primary health care services to increase availability and affordability and to contribute to improve health outcomes including those mentioned in the Millennium Development Goals.

Recognizing that Member States have different domestic legislation, approaches, regulatory responsibilities and delivery models.

Noting that progress in the field of traditional medicine has been obtained in a number of Member States through implementation of the WHO Traditional Medicine Strategy 2002-2005.

Expressing the need for action and cooperation by the international community, governments, and health professionals and workers, to ensure proper use of traditional medicine as an important component contributing to the health of all people, in accordance with national capacity, priorities and relevant legislation.

In accordance with national capacities, priorities, relevant legislation and circumstances, hereby make the following Declaration:

I. The knowledge of traditional medicine, treatments and practices should be respected, preserved, promoted and communicated widely and appropriately based on the circumstances in each country.

II. Governments have a responsibility for the health of their people and should formulate national policies, regulations and standards, as part of comprehensive national health systems to ensure appropriate, safe and effective use of traditional medicine.

III. Recognizing the progress of many governments to date in integrating traditional medicine into their national health systems, we call on those who have not yet done so to take action.

IV. Traditional medicine should be further developed based on research and innovation in line with the "Global strategy and plan of action on public health, innovation and intellectual property" adopted at the Sixty-first World Health Assembly in resolution WHA61.21 in 2008. Governments, international organizations and other stakeholders should collaborate in implementing the global strategy and plan of action.

V. Governments should establish systems for the qualification, accreditation or licensing of traditional medicine practitioners. Traditional medicine practitioners should upgrade their knowledge and skills based on national requirements.

VI. The communication between conventional and traditional medicine providers should be strengthened and appropriate training programmes be established for health professionals, medical students and relevant researchers.

Biomedicines Update

Global norms and standards for biological quality, safety and efficacy

WHO Expert Committee on Biological Standardization

Established in 1947, the Expert Committee on Biological Standardization (ECBS) is one of the longest standing World Health Organization (WHO) committees and has overall responsibility for setting written standards and establishing reference preparation materials. Standards developed through the ECBS relate to the production and quality control of safe and effective biological products. They provide guidance for national regulatory authorities and manufacturers and serve as the standard for prequalification of vaccines for supply to countries through international agencies. Reference preparation materials are available from designated WHO laboratories and provide the basis for comparison of materials used in biologicals worldwide.

Members of the ECBS are scientists from national control agencies, academia, research institutes and public health bodies. These scientists act as individual experts and not as representatives of their respective organizations or employers. The decisions and recommendations of the ECBS are based entirely on scientific principles and public health considerations.

The ECBS reports directly to the WHO Executive Board, which is the executive arm of the World Health Assembly. The outcome of each ECBS meeting is subsequently published in a technical report. This report provides updated information on standards for assuring the quality, safety and efficacy of biological products as well as on the establishment of new or updated WHO international standards for designating the activity of biological substances. ECBS technical reports are available at: http://www.who.int/biologicals/publications/trs/en/index.html

Highlights of the 2008 ECBS meeting

Biological medical products such as vaccines, blood products, biotherapeutics and associated diagnostics save lives, reduce suffering and improve health, but only if these products and technologies are of good quality, are safe, effective, available, affordable and properly used. WHO is working with it's Member States to use only biological medicines of assured quality in national health systems.

The WHO Expert Committee on Biological Standardization (ECBS) establishes global norms and standards that help define products of assured quality. The ECBS meets annually and their most recent meeting was held in Geneva from 13 to 17 October 2008. During the meeting, 57 agenda items were considered. This was accomplished, as in previous years, by running two parallel tracks, one dedicated to vaccines and selected other biological medicines; one dedicated to blood products and related *in vitro* diagnostic devices.

The most important outcomes of the 2008 ECBS meeting were:

Snake antivenom immunoglobulins
A new written standard for production, control and regulation of snake antivenom immunoglobulins was established. Snake antivenom immunoglobulins (antivenoms) are the only therapeutic products for the treatment of envenomings due to snakebite. The lack of availability of effective snake antivenom immunoglobulins to treat specific types of envenomings encountered in various regions of the world has become a critical health issue at global level. The crisis has reached its greatest intensity in sub-Saharan Africa, but other regions, such as South-east Asia, are also suffering from a lack of effective and affordable products.

The complexity of the production of efficient antivenoms, in particular the importance of preparing appropriate snake venom mixtures for the production of hyperimmune plasma (source of antivenom immunoglobulins), the decreasing number of producers and the fragility of the production systems in developing countries further jeopardize the availability of efficient antivenoms in Africa, Asia, the Middle East, and South America. Also, most of the remaining producers are located in countries where the application of quality and safety standards needs to be improved.

The new Guidelines cover all the steps involved in the production, control and regulation of venoms and antivenoms. It is hoped that this document, by covering comprehensively current existing experience in manufacture, control, and preclinical and clinical assessment of these products will serve as a guide to national control authorities and manufacturers to support worldwide production of these essential medicines.

Yellow fever vaccine
An amendment to the written standard for yellow fever vaccine was also established. This requires that the expression of potency of such vaccines be in International Units (IU) per dose. The dose recommended for use in humans shall not be less than 3.0 log10 IU. This new expression of potency should be approved by National Control Authorities, and will also be used as the standard for WHO prequalification of yellow fever vaccines.

Abbreviated licensing pathways for certain biological therapeutic products
The Expert Committee also discussed a proposal to establish abbreviated licensing pathways for certain biological therapeutic products. Control of chronic diseases is a major challenge for public health systems in WHO Member States. Innovative biological medicines developed by modern molecular biological approaches have been successful in treating many life-threatening diseases and the market for these products is rapidly growing.

However, such innovative biological medicines are expensive. This has limited their use, particularly in developing countries. The expiration of patents on key biological drugs such as recombinant insulin, human growth hormone and erythropoietin is opening the door for copies of these drugs to be made by developing country manufacturers. This may contribute to a substantial increase in their availability at an affordable price.

Generic versions of expired-patent chemical drugs are well known. However, copy biological medicines are far more complicated products for which the current generic regulatory pathway is unsuitable. Nevertheless it is essential to ensure that there is appropriate regulatory oversight in place. Regulatory over-

Proposals to establish new or replacement International Standards or WHO reference reagents: October 2008

Name of preparation	*Proposed status*
VACCINES AND RELATED SUBSTANCES	
Influenza H5N1 antibody (human)	Ist International Standard
Human papillomavirus type 16 DNA	Ist International Standard
Human papillomavirus type 18 DNA	Ist International Standard
Rabies vaccine	6th International Standard
Acellular Pertussis vaccine Modified Kendrick Test	Ist International Standard
Pertussis antiserum (human)	Ist International Standard
Pertussis antiserum (human)	WHO Reference Reagent
BLOOD PRODUCTS AND RELATED SUBSTANCES	
Anti-hepatitis B immunoglobulin	2nd International Standard
Blood coagulation factor IX, concentrate	4th International Standard
Factor VIIa concentrate	2nd International Standard
Parvovirus B19 DNA	2nd International Standard
Anti-A and anti-B antibodies, human	WHO Reference Reagents
Anti-hepatitis C core antigen (HBcAg), antibodies, human	Ist International Standard
Extended use for the International Standard for alpha-1-antitrypsin (05/162)	1st International Standard
DIAGNOSTIC REAGENTS AND RELATED SUBSTANCES	
Haemophilia A intron 22 inversion for molecular genetic diagnosis	Ist reference panel
Fragile X syndrome for molecular genetic diagnosis	Ist reference panel
CYTOKINES, GROWTH FACTORS AND ENDOCRINOLOGICAL SUBSTANCES	
Insulin-like growth factor (IGF-1)	2nd International Standard

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Proposals to establish new or replacement International Standards or WHO reference reagents: October 2008 *(Continued)*

Name of preparation	*Proposed status*
ANTIBIOTICS	
Gramicidin	2nd International Standard
ITEMS PROPOSED IN MARCH 2008 BUT SUBSEQUENTLY WITHDRAWN	
Human papillomavirus type 16 antibody (human)	1st Reference Reagent to 1st International Standard
Thromboplastin, human, plain	International Standard
Soluble serum transferrin receptor (STFR), recombinant	Ist International Standard
Vancomycin	2nd International Standard
Parathyroid hormone 1-84, human recombinant	Ist International Standard
Poliovirus type 1 (Sabin) for MAPREC	Ist International Standard

sight should not be so lax that ineffective or dangerous products are allowed into the market place or so restrictive that safe and effective products face regulations that are too stringent.

The ECBS affirmed that reduced data packages may be suitable to provide sufficient assurance about the quality, safety and efficacy of certain products, but it recommended that WHO and countries move forward cautiously. Based on the outcome of discussions and following consideration by the Committee, the ECBS therefore recommended that the current document be strengthened and some issues further clarified. A revised version should be re-submitted to the Committee in 2009.

Global reference preparations

A total of 18 new or replacement global reference preparations were established. These are the primary calibrant against which regional or national measurement standards are benchmarked. An updated list is available at http://www.who.int/biologicals/en/.

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Safety of Medicines

The mobile laboratory: a new concept in medicines surveillance

According to the World Health Organization (WHO), about 6 to 10% of medicines worldwide are counterfeit; a market worth 32 billion US dollars in annual sales. The phenomenon has grown in recent years due to methods of counterfeiting becoming more sophisticated and to an increase in the quantity of counterfeit drugs crossing borders. Trade in fake medicines mainly occurs in developing countries, but counterfeiting is now also increasingly becoming a problem in developed countries.

In response to the challenge presented by the public health crisis caused by a global increase in counterfeit drugs, WHO has launched a special taskforce, the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). The main purpose of IMPACT is to build a coordinated network across and between countries in order to halt the production, trading and sale of fake medicines around the world. IMPACT is a partnership comprising all the major anti-counterfeiting players, including international organizations, nongovernmental organizations, enforcement agencies, pharmaceutical manufacturers associations and drug regulatory authorities.

As elsewhere in the world, fake and substandard drugs in China are driven by huge profits, and have consequently become quite sophisticated. In order to crack down on the manufacturing and marketing of counterfeit pharmaceutical products, the Chinese Government has implemented a number of drug surveillance programs. In China, fake and substandard drugs mainly appear at the retail level in the supply chain, and therefore these programmes generally require samples to be collected from the market and analysed in quality control laboratories at the provincial or district level.

Common methods used on-site by local authorities include basic tests, such as appearance, colour and weight, identification by thin-layer chromatography (TLC), and basic functional group tests using wet chemical analysis techniques. Samples suspected of being counterfeit are then sent to quality control laboratories at the district level for analysis using more specific methods such as high performance liquid chromatography (HPLC). Such programmes have their merits, but are not very effective in detecting the more sophisticated high technology counterfeit products.

To reinforce surveillance, medicines are also routinely sampled from the market and sent to district laboratories for testing, but this can be costly. Moreover, counterfeit drugs are often deliberately made to pass tests defined in the Chinese Pharmacopoeia to avoid being caught by the Chinese State Food and Drug Administration (SFDA) surveillance programme. There is therefore a demand to improve on-site analysis so that more sophisticated counterfeits can be reliably detected, and resources at the district level can be better utilized. Reliable on-site analysis will also allow resources to be efficiently targeted at those cases where

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Mobile laboratories in China

law enforcement already has evidence that counterfeit products are being distributed.

Objectives and development of the mobile laboratories

In January 2003, in response to a call from the SFDA for drug monitoring in predominantly rural areas, the Chinese National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) proposed that mobile laboratories be used for quality testing. The laboratories are specially designed vans equipped to perform various quick analyses. The primary objectives of the mobile laboratories are:

- To utilize the mobility of the laboratories to extend drug surveillance into China's remote countryside.
- To increase consumer confidence in the quality of pharmaceutical products available on the Chinese market.
- To provide quick, easy-to-use, and effective screening methods for on-site drug testing.
- To provide a platform for the deployment of modern high-technology analytical methods that would both aid in the crackdown on the sale and distribution of counterfeit drug products, and provide reliable evidence for law enforcement.
- To reduce the high cost and increase the efficiency of routine drug quality post-marketing surveillance.

On 30 November 2003, less than 10 months after the initial proposal from NICPBP, the first mobile laboratory for drug quality testing was unveiled. On 5 January 2004, the former Vice Premier of China inspected the mobile laboratory and watched a live demonstration of a high technology screening method. The Vice Premier was very impressed with the new technology and the concept of such a mobile laboratory and requested that the Ministry of Finance, the State Committee of Reform and Development and the National Bureau of Quality and Standards provide the programme with full support and assistance.

Operating the mobile laboratory
Currently, the only internationally available system for quick screening of counterfeits on-site is the Minilab test kit, which is capable of testing less than 50 common products, such as antibiotics or antimalarials, but the Minilab test kit is not sufficient to address the problem of counterfeits in China. The scientific equipment in the mobile laboratory includes a near-infrared spectrometer, TLC, colorimetry, digital photography, visible microscopy, and test kits for specific chemical reactions. The main screening tool is based on a near-infrared spectrometer and a pre-developed standard analytical method that uses a library of near-infrared (NIR) spectra (developed by the NICPBP) of all the registered pharmaceutical products in China. This near-infrared based system is quick, accurate, non-destructive, and versatile.

Apart from analytical instrumentation, another important tool in the mobile laboratory is the information system, which includes manufacturer information for officially registered products, including the registration numbers, formulations, dosages and labelling, etc. as well as a list of known counterfeits. Dedicated software for the mobile laboratory allows easy access to the information, even in remote areas. The software is also used to support the near-infrared instruments by providing automatic analysis of the near-infrared spectrum using pre-loaded analysis methods, and generation and logging of all test reports.

In addition, the software includes a database of analytical methods, digital manuals, and predefined standard forms to record and manage mobile laboratory activities such as when and where the mobile laboratories have been dispatched. The mobile laboratory thus combines modern information technology, scientific management systems, and modern analytical instruments that can quickly and non-destructively analyse drug products. The mobile laboratories provide an effective screening tool for the crackdown on counterfeit drugs.

Reliability of the NIR method for drug screening
During 2006 and 2007, mobile laboratories tested a total of 10 340 batches of pharmaceutical products, of which 329 batches were known to be fake. Of the 10 340 batches tested, 1087 (about 10.5%) failed the NIR screening, including all 329 batches that were known to be fake. In addition to the fake products, some non-counterfeit products failed to pass the NIR screening because of changes in product formulations. All products that failed the NIR screening were sent to district laboratories for further testing using more specific methods. These results show that NIR screening is a very reliable method for the detection of counterfeit drugs, and also dramatically decreases the number of products that need to be tested in district laboratories.

Results of using mobile laboratories for drug testing
From April 2004 to November 2005, field tests of the mobile laboratories were carried out in 5 provinces in China: Anhui, Hubei, Hunan, Sichuan and Yunnan. Suitability, accuracy and efficiency of the analytical equipment was evaluated under real conditions. The evaluation included the effect of vibration on the equipment when the van was driven on rough roads in the countryside. Field tests were used to look for possible areas for improvement.

As an example of these trials, starting in August 2004, a mobile laboratory was dispatched 165 times in Zhumadian Prefecture of Henan Province. The mobile laboratory visited 8 of 11 counties in the prefecture as well as 42 of 186

villages, and covered a total distance of 17 000 km, including highways between cities and rough roads in the countryside.

The mobile laboratory examined a total of 260 pharmacies and clinics and screened 3965 batches of 408 different drug products. Of these, 57 batches were suspected to be fake and were further tested by analytical methods in district laboratories resulting in five batches that were confirmed as counterfeit. The mobile laboratories also visited AIDS prevention stations in Zhumadian Prefecture, clinics in all 24 villages with a high population of AIDS patients, and in all nine villages with a moderate population of AIDS patients. No fake or substandard drugs were found in the 1347 batches that were tested. The extensive surveillance that is possible with mobile laboratories thus ensures the quality and safety of drug products used by at-risk groups such as AIDS patients.

To date, 379 mobile laboratories have been deployed across China. They have visited over 77 000 drug dispensaries, and have travelled over 2 000 000 km. They have screened more than 379 000 batches of drugs, of which approximately 37 000 were suspected of being fake or substandard. Of these, approximately 14 000 batches were later confirmed to be counterfeit. The average analysis cost per batch in the district laboratory is about 600 RMB. If the traditional test programme were used for the 379 000 batches, they would have cost almost 230 million RMB. The new, targeted analysis of only those batches that were suspect based on pre-screening results reduced the cost of analysis in the district laboratories by about 90%, to approximately 22 million RMB.

These data show that the mobile laboratories not only increase the successful sampling rate and improve the efficiency of the drug surveillance programme, but also result in significant cost-savings. Currently, the mobile laboratory programme covers about 80% of essential medicine products commonly used in rural areas.

The mobile laboratory programme has also shown its utility in response to emergencies caused by fake drugs. As an example, in the summer of 2006, instead of propylene glycol, the toxic ingredient diethylene glycol was used by mistake in a few batches of Armillarisin A® for injection, resulting in 11 deaths. Immediately after the incidents were reported, the mobile laboratories were dispatched to screen all suspected products that were still on the market. Gas chromatography (GC) was later used to verify the results for medicines screened positive for diethylene glycol by the mobile laboratories. In this case, the NIR-based quick screening method demonstrated 100% accuracy.

Future development of the mobile laboratory programme

A second generation of mobile laboratories is currently under development which incorporate a patented green HPLC system that is suitable for mobile operation. The key to this new HPLC is that the solvents are close-loop recycled inside the van. The advantage of implementing the HPLC system in the mobile laboratory is that if a drug product tests positive using the NIR-based prescreening method, then an on-site verification can be performed immediately.

Incorporating the HPLC technology should further improve the accuracy and efficiency of the mobile laboratory programme, especially in remote areas where the local Food and Drug Administration or other analytical laboratories are far away. A combination of the NIR-based quick and non-destructive screening method and on-site verification capability using the new HPLC technology may also

play an important role in counterfeit drug detection in many developing countries.

Conclusions

The mobile laboratory is a new monitoring system that provides in-time information gathering, quick screening, targeted sampling based on drug law-enforcement efforts, and accurate analytical tests. These mobile laboratories have demonstrated considerable success in ensuring medicines safety. The laboratories have increased the efficiency of the drug surveillance programme and reduced costs. They have also expanded the monitoring area of the programme and have improved the ability of the authorities to rapidly respond when there is evidence of adverse reactions to drug products on the market. In the future, mobile laboratories will continue to play an important role in increasing the efficiency of government efforts to crack down on the manufacture and marketing of counterfeit products in China.