World Health Organization

WORKING GROUP OF MEMBER STATES ON SUBSTANDARD/SPURIOUS/FALSELY-LABELLED/ FALSIFIED/COUNTERFEIT MEDICAL PRODUCTS
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WHO's role in measures to ensure the availability of good-quality, safe, efficacious and affordable medical products

1. Medicines are essential for the provision of both curative and preventive health care. In most countries, medicines are second only to salaries in size as a component of health expenditure, constituting between 15% and 30% of public health budgets in most low- and middle-income countries. In such countries the purchase of medicines also represents the largest component of private household expenditure. The present report is focused on WHO's role in ensuring the availability of good-quality, safe, efficacious and affordable medical products.[1]

2. Surveys undertaken in over 50 countries have revealed that essential medicines for the treatment of acute diseases are only available at 56.1% of health-care facilities in the public sector and at 65.6% of those in the private sector. In the case of chronic diseases, ensuring equitable and regular access to essential medicines is proving even more difficult, and here availability is only 36.0% and 54.7% respectively. Low public-sector availability of essential medicines forces patients into the private sector, where medicines are often two or three times more expensive. Private-sector preference for originator brand products further increases the price and makes treatment even harder to afford. For example, in Ghana one month of oral diabetes treatment costs the equivalent of eight days' minimum wage (i.e. over 25% of the minimum monthly wage). In most low- and middle-income countries patients with diabetes, who live on US$ 1 or US$ 2 per day respectively, would need to spend between 25% and 50% of their monthly income to buy one vial of insulin from a private pharmacy.

3. Problems with the quality of medicines are widespread. Recent studies have produced the following results for one African country: of four samples of isoniazid tablets tested, four failed quality tests; of three samples of pyrazinamide tablets tested, three failed; of 15 samples of rifampicin capsules tested, five failed; and of 19 samples of streptomycine injections tested, 10 failed. The studies also revealed that in six African countries, 73 samples of non-WHO prequalified antimalarials out of 184 (39.7%) failed quality testing, compared with only three WHO-prequalified samples out of 83 (3.6%); and that of 55 generic manufacturers of family planning combination tablets, fewer than one third would pass evaluation by the WHO/United Nations prequalification programme. With regard to prescribing, globally fewer than 50% of prescriptions follow national clinical practice; in most

[1] See document A/SSFFC/WG/3 for information on WHO's work against substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Such products are referred to hereinafter by the term "counterfeit". See document A/SSFFC/WG/4 for details of WHO's involvement with the International Medical Product Anti-Counterfeit Taskforce.

countries, fewer than half the patients adhere to the prescribed treatment. Thus, irrational use by prescribers and patients leads to suboptimal treatment and huge economic waste.

4. WHO's work in this area is principally focused on three objectives, namely, the promotion of: (i) universal availability of, and access to, essential medicines; (ii) assured quality and safety of medicines; and (iii) rational use of medicines. In each of these three technical areas WHO is conducting public-health advocacy, performing global normative functions and providing technical support at country level. As the United Nations specialized agency for health, WHO's responsibility for developing, establishing and promoting international standards with regard to pharmaceutical products is described in the Constitution of the World Health Organization and has existed for over 60 years. For example, every year over 100 new generic names are assigned by WHO and some 60 new or updated global quality standards are set (see below). This activity includes the development of global quality standards for new generic medicines for which there are no originator products, such as generic combination tablets for HIV/AIDS and formulations for malaria suitable for children.

5. Advocacy of the essential medicines concept and the provision of technical support to Member States in developing and implementing national medicines policies and programmes started in 1977 when the first WHO Model List of Essential Drugs was published.[1] The Declaration of Alma-Ata of 1978 recognized essential medicines as one of the eight components of Primary Health Care, and in 1981 the WHO Action Programme on Essential Drugs was established. Currently, WHO provides individual technical support to over 100 Member States, with full-time pharmaceutical advisers in over 40 low- and middle-income countries.

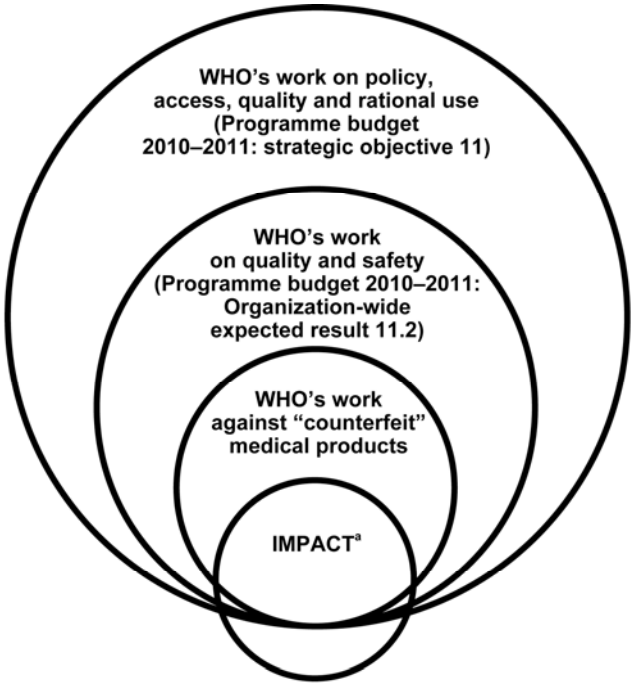
WHO'S WORK IN SUPPORT OF ENSURING THE QUALITY, SAFETY AND EFFICACY OF MEDICINES

6. The main activities undertaken in recent years and the achievements recorded are described below.[2] The relationship between the three areas of activity of WHO's medicines programme is represented in the Figure below.

[1] As part of the revised procedure for updating the Model List, presented to the Executive Board in document EB109/8, the term "essential medicines" is now used in preference to "essential drugs".

[2] See also the Essential Medicines Biennial Report 2008–2009 (document WHO/EMP/2010.1).

Figure. Areas of activity within WHO's medicines programme



[a] "IMPACT" refers to the International Medical Products Anti-Counterfeiting Taskforce

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Global normative activities

7. WHO is responsible for the following unique global normative activities, all of which need to be performed on a continuous basis.

- International Nonproprietary Names[1] have been selected for all new active pharmaceutical ingredients since the adoption by the Health Assembly in 1950 of resolution WHA3.11 (between 100 and 120 selections per year).

- The Anatomical Therapeutic Chemical with Defined Daily Doses classification system has been applied for all new active pharmaceutical ingredients since 1975 (between 100 and 120 ingredients per year).

- Since the establishment of the Interim Commission in 1946,[2] the classification of new substances has been undertaken under various international treaties for the control of dependence-producing substances (between three and five substances every two years).

[1] See paragraph 9 below for fuller information on International Nonproprietary Names.

[2] The Interim Commission of WHO took up the health-related work of the League of Nations. WHO is the specialized agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, and the United Nations Convention on Psychotropic Substances, 1971.

- Global quality-control standards have been set since 1946; they include monographs for inclusion in *The International Pharmacopoeia* with international chemical reference standards for all new essential medicines (between 20 and 50 new or updated specifications per year). Global quality-assurance standards have also been set since 1946; these include good manufacturing practices, good laboratory practices for quality-control laboratories and regulatory guidance, including stability requirements for pharmaceutical products (a total of 56 guidelines are maintained; there are between five and 10 new or updated standards per year).

- Global standards on quality and safety of blood products, in vitro diagnostics and other biologicals have been developed since the 1950s (between five and 10 new or updated standards per year).

- WHO has been managing since 2001 the prequalification, for United Nations procurement, of priority medicines for HIV/AIDS, tuberculosis, malaria and reproductive health (between 40 and 50 new products per year).

- The International Conference of Drug Regulatory Authorities has been organized every two years since 1980 (attendance: over 100 Member States).

- A monthly notification has been provided since 1981 to national information officers concerning recent regulatory decisions taken by Member States in respect of medicines safety. Since 1988 it has been published as the *WHO Pharmaceuticals Newsletter*.

- *WHO Drug Information* has been published on a quarterly basis since 1986, providing summaries of regulatory decisions, draft quality specifications (for wide consultation) and International Nonproprietary Names.

- WHO Model List of Essential Medicines, with a separate list for children, has been compiled and maintained since 1977. A new edition is issued every two years.

- WHO Model Formulary has been issued every two years since 2004.

- *The world medicines situation*, which provides detailed country and global statistics, has been published in two editions (1988 and 2004). A further review is due to be printed in 2011.

8. **International Nonproprietary Names and methodological developments.** An International Nonproprietary Name (INN) is a generic name assigned to an active pharmaceutical ingredient, either chemical or biological, that is public property and globally recognized. No new medicines can be marketed without an INN assigned by WHO. The INNs facilitate the exchange of information among all parties involved in medicines research, production, regulation and use; they are important product identifiers in pharmacovigilance systems. Assigning new INNs is therefore a unique and essential function of WHO. During the biennium 2008–2009, WHO assigned and published 254 proposed INNs (172 chemicals and 82 biologicals) and 255 recommended INNs (177 chemicals and 78 biologicals), through a broad consultative process.[1] The cumulative total stood at 8199 INNs in seven languages at

[1] For the procedure for the selection of recommended international nonproprietary names for pharmaceutical substances, see Annex 1 in WHO Technical Report Series, No 581, 1975. The original text of the procedure was established by the Executive Board in resolution EB15.R7; it was later revised by resolutions EB43.R9 and EB115.R4.

the end of 2009. An INN nomenclature scheme has recently been adopted for monoclonal antibodies. The new web-based INN integrated data management information system – the publicly accessible part of which is available on WHO's collaborative workspace, MedNet – offers online INN consultation and an integrated publication process.

9. **Global quality standards for medicines.** Global norms and standards are essential for the development and production of pharmaceuticals in any part of the world, whether they be originator or generic products. Such standards may have considerable commercial implications and their independent development is therefore guaranteed by highly standardized procedures[1] and careful identification and management of potential conflicts of interest. Expert Committee reports are among WHO's most authoritative normative statements.

10. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is convened annually to develop and update global pharmaceutical norms and quality standards. The first meeting was held in 1947.[2] Meetings of the Committee were originally held every two years but since 2004 the Committee has been convened every year in order to cope with the increasing demand for timely and up-to-date global normative materials. The reports of meetings held in 2008[3] and 2009[4] include 11 new and revised quality-assurance guidelines for WHO good manufacturing practices, including those for sterile pharmaceutical products, active pharmaceutical ingredients and pharmaceutical products containing hazardous substances. In addition, the WHO good distribution practices for pharmaceutical products and WHO good practices for quality-control laboratories were revised. Guidelines for the preparation of a contract research organization master file, and for the requalification of prequalification dossiers were also finalized, together with regulatory guidance on stability-testing requirements. The procedure for the prequalification of pharmaceutical products was revised and a new procedure developed for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. In addition, during these two Expert Committee meetings, 66 new monographs for inclusion in *The International Pharmacopoeia* were adopted, together with 16 related International Chemical Reference Substances.

11. Work on global quality standards for medicines is carried out in a transparent manner, following a strict consultative process and in collaboration with many partners, including those listed below:

- national and regional authorities
- international organizations (e.g. WIPO, WTO, UNICEF, UNFPA, UNAIDS, the World Bank and the World Customs Organization)
- international professional and other associations, nongovernmental organizations, including consumer associations and industry (e.g. MSF International, the International Federation of

[1] See Regulations for expert advisory panels and committees. *Basic documents,* 47th ed., Geneva, World Health Organization, 2009. Additional guidance is laid down in the WHO Manual.

[2] First named the Expert Committee on the Unification of Pharmacopoeias, in 1951 the Committee was renamed the Expert Committee on the International Pharmacopoeia; since 1959 it has been named the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

[3] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953).

[4] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957).

Pharmaceutical Manufacturers and Associations, the International Generic Pharmaceutical Alliance, the World Self-Medication Industry, the International Pharmaceutical Federation and the World Medical Association)

- members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations
- specialists from all quality assurance-related areas, including regulatory bodies, universities and industry
- WHO Collaborating Centres, which are subject to the official nomination process. These are usually national quality-control laboratories
- pharmacopoeia commissions and secretariats, national institutions and institutes
- regional and interregional groups (e.g. the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; and ASEAN).

12. The independent quality standards and guidelines referred to above enable WHO Member States and other parties to meet the challenges of increasing globalization; they are implemented and used both by Member States and within the WHO-managed United Nations programme on prequalification of medicines. The development of quality-control specifications, i.e. monographs for inclusion in *The International Pharmacopoeia*, focuses on new essential medicines and those of major public health need, including medicines for HIV/AIDS and related conditions, and medicines for malaria and tuberculosis, together with medicines such as oxytocin, mebendazole and oseltamivir phosphate, with their respective dosage forms. Development work also concerns radiopharmaceuticals and numerous monographs that apply to paediatric formulations. The WHO guidelines for regulatory guidance on stability testing are now on the web sites of national, regional and interregional regulatory authorities in Europe, and on those of their counterparts in Japan and the United States of America, demonstrating recognition of WHO as the global standard-setting organization and constituting a significant step towards the harmonization of regulatory requirements.[1]

13. **Global reporting on the safety of new medicines in public health programmes.** Medicines are often approved for marketing when their full safety pattern is not yet known. For this reason, careful pharmacovigilance is needed especially in the first few years after introduction. For new medicines for HIV/AIDS and malaria, special provisions are needed as most of the medicines concerned are used in countries where pharmacovigilance systems are not fully developed. The application of pharmacovigilance for the detection, assessment and prevention of adverse drug reactions improves patient care and safety.

14. Since 1975 the WHO Programme for International Drug Monitoring, together with the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden), has been facilitating the rapid identification and communication of adverse drug reaction signals via a global electronic database. During the biennium 2008–2009, 30 such signals were published. By the end of 2009, the

[1] For further information please refer to the web sites of WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use at the following addresses: http://www.who.int/medicines/en/ and http://www.ich.org (accessed 7 January 2011).

database contained over 5 million individual case reports. With the addition of seven new countries,[1] the Programme now has 96 full member countries. As a result, the Programme has an increased ability to collect adverse drug reaction reports globally; this includes the capacity for rapid global collection of safety information on new vaccines against pandemic influenza or new essential medicines to treat HIV/AIDS, tuberculosis and malaria.

15. Training courses and workshops on pharmacovigilance, and on adverse drug reactions and their monitoring have been held in both English and French. Following the course on the principles of "active surveillance", which was organized in July 2007 in Accra, two Cohort Event Monitoring Programmes started to provide safety information on new antimalarial medicines. PaniFlow, a new tool for monitoring adverse events during influenza pandemics, following either immunization with vaccines or treatment with medicines, has been developed by the WHO Collaborating Centre in Uppsala, together with the Swiss regulatory authority for medicines. The tool has been made available to countries using vaccines donated by WHO.

16. **Quality and safety of blood and blood products.** Blood products and associated diagnostics help to save millions of lives every year.[2] It is essential that these products and technologies are of good quality, and that they are safe, effective and readily available. A number of medicinal products derived from blood and plasma are included in the WHO Model List of Essential Medicines. The Secretariat works with Member States to strengthen regulatory systems in support of the goal of using only blood-derived medicines of assured quality in national health systems.

17. Since the 1950s WHO's biological reference preparations for blood products and related in vitro diagnostics have been providing guidance for national regulatory authorities and manufacturers on production and quality control for safe and effective products. During the biennium 2008–2009 reference preparations for genotypes of hepatitis B virus were developed; these will help to improve the quality of diagnostic and tracking devices for the control of the disease. Reference materials for the control of blood products and the diagnosis of genetic diseases such as haemophilia were also prepared. Additionally, 18 new or replacement global reference preparations were developed, providing a benchmark for industries to develop diagnostics and for regulators to control them.[3]

18. In May 2010, the Health Assembly adopted resolution WHA63.12 on the availability, safety and quality of blood products. This resolution aims to help developing countries to increase the availability of safe blood products by advocating the need to provide support to blood establishments for their implementation of validated quality and safety standards. The goal is to strengthen regulation of blood products under the scope of the medicines regulatory authorities and to improve blood establishments' processing capacity for the preparation of blood components, including plasma for fractionation. In order to achieve this, quality-assurance systems and good manufacturing practices will need to be implemented in blood establishments, regulatory oversight will need to be enforced for all blood products and the technical capacity of regulatory authorities and control laboratories will need to be strengthened. The WHO Achilles project has been developed in order to direct the Secretariat's support for implementation of the resolution.

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[1] Botswana, Madagascar, Montenegro, Namibia, Saudi Arabia, Senegal and Sudan.

[2] The term "blood products" as defined by the Expert Committee on Biological Standardization, is set out in resolution WHA63.12 as follows: "any therapeutic substances derived from human blood, including whole blood, labile blood components and plasma-derived medicinal products".

[3] See http://www.who.int/biologicals/expert_committee/ECBS%20Outcomes_2008.pdf (accessed 10 January 2011).

19. **Production, control and regulation of snake antivenoms.** There is a lack of effective snake antivenoms to treat the specific types of envenomings encountered in various regions of the world following snakebites. This is a critical but neglected global health issue. WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins have been issued in order to help manufacturers and regulators to ensure that only good-quality, effective antivenoms reach patients.[1] Training and technical assistance have been provided to regulatory authorities and manufacturers from 34 countries.

TECHNICAL SUPPORT FOR MEDICINE REGULATION AND QUALITY ASSURANCE IN COUNTRIES

20. **International information exchange: 13th International Conference of Drug Regulatory Authorities.** The key international meeting of medicine regulatory agencies is the biennial International Conference of Drug Regulatory Authorities, which is convened and co-hosted each time by WHO and the Government of a Member State. The first International Conference took place in 1980. The 13th Conference, which was held in Berne in 2008, brought together over 300 representatives from 96 countries.[2] During the week-long meeting regulators discussed and adopted recommendations for assuring the quality, safety and efficacy of medical products. The following subjects were included: better collaboration and information exchange among regulators; safety and pandemic preparedness; strategies to fight "counterfeit" medicines; innovative ways of regulating medicines for children; and regulation of blood products, biosimilars and radiopharmaceuticals. A preliminary meeting on better medicines for children focused on challenges to, and opportunities for, regulation in support of improved access to safe, good-quality medicines. The latest International Conference was held in Singapore from 30 November to 3 December 2010, with a preliminary meeting organized on regional regulatory collaboration.

21. **Regulatory support to countries.** All WHO's normative work in the area of quality, safety and efficacy is intended to support national medicine regulatory authorities and is developed with them through the global consultative processes referred to above. In addition, since the 1970s many other activities have been conducted as part of the provision by WHO of direct support to individual regulatory agencies (e.g. through independent assessments, consultancy support, training and international exchanges). Increasing globalization and more complex manufacturing and product specifications have created additional challenges for national medicine regulatory authorities and manufacturers. As a consequence, national regulatory capacity needs to be regularly assessed using a standardized WHO tool. During the biennium 2008–2009, assessments were conducted on 20 national medicine regulatory authorities. By the end of 2009, a total of 46 such authorities were officially assessed by WHO.[3]

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[1] Available online at http://www.who.int/bloodproducts/snake_antivenoms/snakeantivenomguideline.pdf (accessed 12 January 2011). WHO's web site also contains information on the worldwide geographical distribution of venomous snakes with details on where the venomous snakes are located, what they look like, which antivenoms are appropriate, and where they can be obtained.

[2] See http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/Recommendations_13ICDRA.pdf (accessed 10 January 2011).

[3] The following Member States were assessed in the biennium 2008–2009: Argentina, Bangladesh, Benin, Burundi, Central African Republic, Chile, Colombia, Congo, Cuba, Democratic Republic of the Congo, Djibouti, Egypt, Gabon, Kyrgyzstan, Niger, Seychelles, Sudan, Turkmenistan, Uganda and Yemen.

22. In response to the need for continuous learning of the staff of national medicine regulatory authorities, WHO has delivered training courses on the assessment of quality, safety and efficacy in the marketing authorization process in all WHO regions, involving participants from over 50 Member States. In order to support the work and decision-making processes of national regulatory authorities, a model for medicines regulation – the WHO Medicines Regulatory Package – has been developed, field-tested and implemented in seven African countries as a tool for exchange of regulatory information and for building regulatory capacity.[1]

23. The African Medical Products Regulatory Harmonization Initiative has been established in response to the increased responsibilities placed on national regulatory systems. WHO is working with the Department for International Development of the United Kingdom of Great Britain and Northern Ireland, the World Bank, the Bill & Melinda Gates Foundation and the Clinton Foundation to improve health in Africa by increasing the availability of medical products that meet standards for safety, efficacy and quality through regional regulatory harmonization. The issue was discussed at the Second African Medicines Regulatory Authorities Conference (Maputo, 16–18 November 2009) which brought together 54 heads and staff of national medicine regulatory authorities from 40 countries. A World Bank Trust Fund has been established to pool donors' contributions to the initiative.

24. WHO has continued to work closely with the national medicine regulatory authorities of Member States from all WHO regions in facilitating information exchange and knowledge transfer. Cooperation with regional networks – such as DRUGNET, which concerns the Newly Independent States – has enabled regulatory support to be provided to a large number of countries. Training has been offered to inspectors in conducting inspections of good manufacturing practices, while quality-control laboratories have received training in good practices for managing pharmaceutical laboratories in order to achieve a good level of quality assurance. Numerous capacity-building workshops have been organized with regulators, including workshops on new pharmaceutical legislation and on regulating medicines promotion.

25. **Prequalification of priority medicines through the WHO/United Nations prequalification programme.** Before 2000, most United Nations agencies and the World Bank used different quality standards in their procurement programmes. Since 2001 the WHO/United Nations prequalification programme has been assisting United Nations procurement agencies and others, supporting them to standardize and promote the quality of priority medicines for treating HIV/AIDS, tuberculosis and malaria and for supporting reproductive health. The programme also helps to maximize the use of funding for these treatments by stimulating the supply of good-quality generic medicines and encouraging fair competition. During the biennium 2008–2009, the programme prequalified 84 medicines, including 14 paediatric formulations and – for the first time – involving reproductive health and influenza products. By the end of 2009 a cumulative total of 239 products had been prequalified. Additionally, nine laboratories were prequalified and 32 training workshops were organized for 659 manufacturers, 583 regulators, and 54 laboratory staff. A new business plan for the programme, completed by a leading firm of management consultants, will help to direct the programme in the coming years. The plan states that, in the context of the current disease landscape, the programme "has a vital, pivotal and ongoing role" and projects an economic return on investment of 170:1 for the period 2009–2013.

[1] See http://infocollections.org/medregpack/interface/home.htm (accessed 10 January 2010).

26. The greatest number of prequalified medicines are manufactured in the South-East Asia Region, but medicines prequalification activities are expanding in other regions, including the Eastern Mediterranean Region. Quality-control laboratories are now being prequalified in Member States in all regions. In China the medicines prequalification team is collaborating with the Government with a focus on improving the quality of fixed-dose combination medicines against drug-resistant tuberculosis. Recently a programme was started for the prequalification of selected active pharmaceutical ingredients. Other programmes, which focus on the prequalification of vaccines, diagnostics, reproductive health devices and insecticide-impregnated bednets, are not discussed in the present report.

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