

## **SECTION I**

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# **THE INTERNATIONAL LANDSCAPE OF QUALITY**



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# GLOBAL DISEQUILIBRIUM OF QUALITY

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## INTRODUCTION

Medicines have a long history and the concepts of how their quality should be tested and regulated have evolved gradually over time. Mithridates VI (120 BC), King of Pontus, concocted a compound preparation called “*Mithridatium*”, which included 41 individual components and was held as a panacea for almost all diseases until as late as the 1780s. It took until 1540 when in England the manufacture of Mithridatium and other medicines was subjected to supervision under the Apothecaries Wares, Drugs and Stuffs Act. The Act was one of the earliest British statutes on the control of medicines and it established the appointment of four inspectors of “*Apothecary Wares, Drugs and Stuffs*” (Griffin and O’Grady, 2003). This could be seen as the start of pharmaceutical inspections. History of Pharmacopoeias, the official books of drug quality standards, probably dates back to one of the proclamations of the Salerno Medical Edict, issued by Fredrick II of Sicily (1240), and ordered apothecaries to prepare remedies always in the same way – *forma curiae*. The first Pharmacopoeias as we know them today started to appear in Europe from the 16th century, e.g., the first Spanish Pharmacopoeia was issued in 1581. The standards for the manufacture of Mithridatium were established in England in *The London Pharmacopoeia* in 1618 (Griffin and O’Grady, 2003).

The modern medicines regulation started only after breakthrough progress in the 19th century life sciences, especially in chemistry, physiology and pharmacology, which laid a solid foundation for the modern drug research and development, and

started to flourish after the Second World War. Unfortunate events throughout recent history have catalysed the development of medicines regulation. In 1937, more than 100 people in the United States died of ethylene glycol poisoning following the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing. This helped to finalize the pending legislation and brought about The Federal Food, Drug and Cosmetic Act with the introduction in 1938 of a pre-market notification requirement for new drugs.

The second catastrophe that influenced the development of drug regulation far more than any event in history was the thalidomide disaster. Thalidomide was a sedative and hypnotic that first went on sale in Western Germany in 1956. Between 1958 and 1960 it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia and other deformities. The role of this disaster in shaping the medicines regulatory systems is not difficult to underestimate. As a result the whole regulatory system was reshaped in the UK, where a Committee on the Safety of Drugs (CSD) was started in 1963, followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964. In the US, The Drug Amendments Act of 1962 was passed by Congress requiring the Food and Drug Administration (FDA) to approve all New Drug Applications (NDA) and, for the first time, demanded that a new drug should be proven to be effective and safe. Of equal importance, the FDA was also given the authority to require compliance with current Good Manufacturing Practices (cGMP), to officially register drug establishments and implement other requirements. The EEC Directive 65/65/EEC, on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products, was also induced by the thalidomide disaster.

It took almost ten years for the European Community (EC), since Council Directive 65/65/EEC was introduced, to further develop harmonization in the Community. In 1975, two Council Directives were introduced, the first on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [75/318/EEC], and the second on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products [75/319/EEC]. The latter established an 'old' Committee on Proprietary Medicinal Products (CPMP) as an advisory committee to the EC and introduced the multi-state procedure known now as the Mutual Recognition Procedure. Directive 87/22/EEC introduced the concentration procedure which is now known as the Centralized Procedure. These directives, and following Council regulation, were the landmarks for starting harmonization inside the European Union (EU) with the final longstanding aim of creating a 'common market' for medicines. The Council Regulation EEC/2309/93 established the European Medicines Evaluation Agency (EMA) in 1993 and re-established the CPMP as a 'new' CPMP to formulate the opinion of the Agency on questions relating to the submission of applications and granting marketing authorizations in accordance with the centralized procedure.

Somewhat parallel with the ongoing harmonization and movement towards creating a common market for medicines inside the EU, the need for wider harmonization was recognized after preliminary contacts between officials from Japan, the EU and the US discussed during the International Conference of Drug Regulatory Authorities (ICDRA – organized by WHO every second year, see below) in Paris in 1989. The preliminary informal discussions had revealed a need for the harmonization of requirements relating to the new innovative drugs and the green light given in Paris led to the establishment, in 1990, of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan and the US with observers from the World Health Organization (WHO), European Free Trade Association (EFTA) and Canada.

## WHO'S CONTRIBUTION TO MEDICINES QUALITY

The WHO was established in 1948 as a specialized agency of the United Nations (UN) serving as the directing and coordinating authority on international health matters and public health. The objective of WHO is “*the attainment by all peoples of the highest possible level of health*” (Article 1 of WHO Constitution), of which the safety, efficacy and quality of medicines are important aspects. One of WHO's functions is “*to develop, establish and promote international standards with respect to ... biological, pharmaceutical and similar products*” (Article 2 of WHO Constitution). WHO aims to promote “*improved standards of teaching and training in the health, medical and related professions*” (Article 2 of WHO Constitution). Based on its mandate, WHO has issued norms and standards, particularly for quality and safety of medicines. In the early stages of its development WHO tried to address quality, safety and efficacy for all medicines. At that time, several innovative guidelines were prepared by using international experts e.g., Principles of testing preclinical drug safety in 1966 (WHO, 1966).

However, the focus was moving more towards meeting developing country needs, especially in the area of quality. The Third World Health Assembly in 1950 approved the publication of *Pharmacopoea Internationalis*. The first edition was published in two volumes (1951 and 1955), with a supplement in 1959 and altogether included 344 monographs on drug substances, 183 monographs on dosage forms and 84 tests, methods and general requirements. Later it was called “*The International Pharmacopoeia*” and its purpose was again considered to be more focused on the developing country needs (1975). After issuing the first WHO Essential Drugs List in 1977 (WHO, 1977), the drugs appearing in *The International Pharmacopoeia* were selected from that list. At the International Conference on Primary Health Care in Alma-Ata in 1978 the supply of essential drugs of good quality was identified as one of the prerequisites for the delivery of health care. The WHO Essential Drugs List was,

until recently, based on generic drugs (Laing et al., 2003) which also explains why WHO has been concentrating mostly on quality assurance of generic drugs. The monographs contained in *The International Pharmacopoeia* were to be used in any country or setting. For this purpose, they are designed to cater for both high-technology methods of testing, or when these are not available, for alternative methods which are less technically demanding. The latest, the fifth volume of the third edition of *The International Pharmacopoeia*, was published in 2003 (WHO, 2003a) and is unique in that it includes all artemisin-based antimalarials known to date.

Nowadays, Good Manufacturing Practices (GMP) are considered an essential element of a comprehensive Quality System, Quality Assurance unit and other quality systems for pharmaceuticals. The first WHO GMP text to be published was developed during 1967–69 and revised in 1975. In 1969, the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in its resolution WHA22.50 (1969) and accepted the GMP text as an integral part of it. The revised versions of both the Certification Scheme and the GMP text were adopted in resolution WHA28.65 in 1975. The next revised and expanded GMP guidelines were prepared during 1989–90 and published in 1992 (WHO, 1992). In 1999, all the WHO GMP texts were collated and published in a separate book titled *Quality Assurance of Pharmaceuticals, Volume 2* (WHO, 1999a). Since then, various amendments have been done to the WHO GMP – the latest in 2002 (WHO, 2002a) and 2003 (WHO, 2003b), respectively. A guidance text on how to apply the concept of application of hazard analysis and critical control (HACCP) methodology to pharmaceuticals was also published in 2003 (WHO, 2003b).

Two other important publications collating WHO's work on assuring quality of generic drugs and responding to the World Health Organization resolutions, adopted in 1971 [EB47.R29] and in 1984 [WHA37.23] referring to the organization's role in "the establishment of internationally acceptable basic requirements for drug registration" should be mentioned. The first was *Quality Assurance of Pharmaceuticals, Volume 1*, published in 1997 (WHO, 1997). This book included a wide range of materials relating to national drug regulations, product assessment and registration, *The International Pharmacopoeia* and related activities, international trade in pharmaceuticals and their distribution, quality control laboratories, counterfeit products, and basic tests for pharmaceutical products. The second was *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products* which was published in 1999 (WHO, 1999b). This popular book among developing country regulators contained general provisions and prerequisites for regulatory control and operating activities, guiding principles for small Drug Regulatory Authorities, principles of review of applications for marketing authorization of generic medicines including guidelines for stability testing and establishing interchangeability (bioequivalence guidelines).

More detailed updates on the WHO activities and guidance documents relating to the quality assurance of medicines are available from the Essential Drugs and Medicines Policy Department (website: <http://www.who.int/medicines/>).

## PHARMACEUTICAL GAPS

Much progress has been achieved over the last 50 years in the field of pharmaceuticals, both in terms of introducing new medicines and improving the regulation of medicines. This progress involves mostly industrialized developed countries where citizens can benefit from new innovative drugs. However, lack of access to quality essential drugs remains a serious global health problem (Pécoul et al., 1999).

We have the medicines to save people from infectious diseases like human immunodeficiency virus (HIV), tuberculosis, malaria and a number of other infectious diseases, yet millions continue to die each year due to lack of access to medicines. We have the medicines to treat major non-infectious diseases as well but in many parts of the world the access to these drugs may be even worse than for anti-infectious medicines.

Medicines are a public good and not simply just another commodity: first for their high social value, and then because consumers and prescribers are unable to assess their quality, safety and efficacy

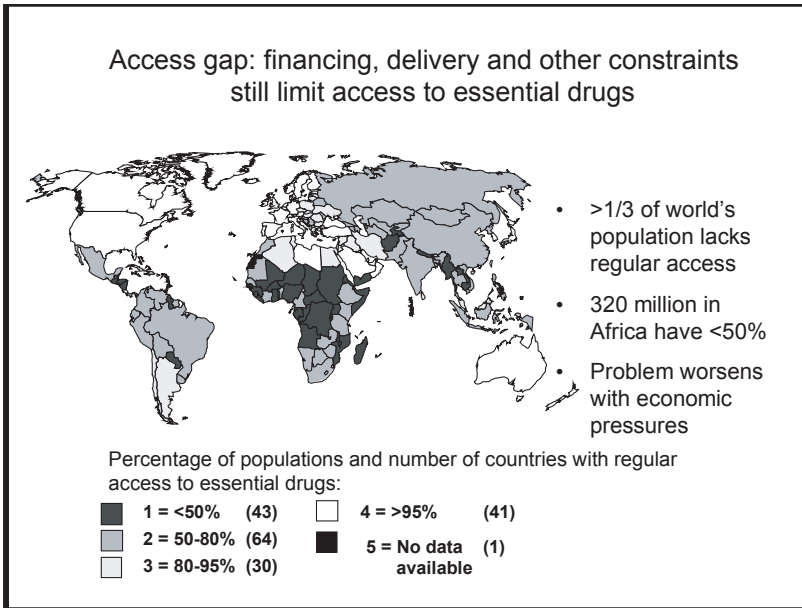
*Dr Gro Harlem Brundtland  
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The high social value of medicines is determined by the contribution they can offer to improve the lives of millions who will otherwise suffer without need, or be unable to contribute to, the development of the societies. It is believed that bad health is contributing to the poverty and is an obstacle for social and economical development.

### Access Gap

Many 'pharmaceutical gaps' do exist worldwide, the most devastating being the access gap. Drugs offer a simple, cost-effective solution to many health problems provided they are available, affordable, and properly used. Despite the global abundance of pharmaceutical products and the sophistication of the pharmaceutical trade, there is still a mammoth gap between those who have, and those who do not have, access to essential drugs.

**Figure 1.1. Access Gap Illustrating the Percentage of Those Countries With Regular Access to Essential Drugs**



Of the 41 countries within the developed world, more than 95% of their populations have regular access to essential drugs. In marked contrast, of the 43 countries in the developing world, 'less than 50%' of their populations have regular access to essential drugs. The severity of the problem can be illustrated more forcefully (Fig. 1.1) by looking at population figures in Africa, where 320 million people fall within the less than 50% classification. The high cost of medicines, plus expensive and often complicated transportation, limits the drug market to countries and populations who can afford to pay, and excludes those who cannot. In times of worsening economic pressures, developing countries with already wilting and limited financial resources become even less able to participate in this market and, subsequently, their impoverished populations are further denied access to essential drugs.

## Population/Consumption Gap

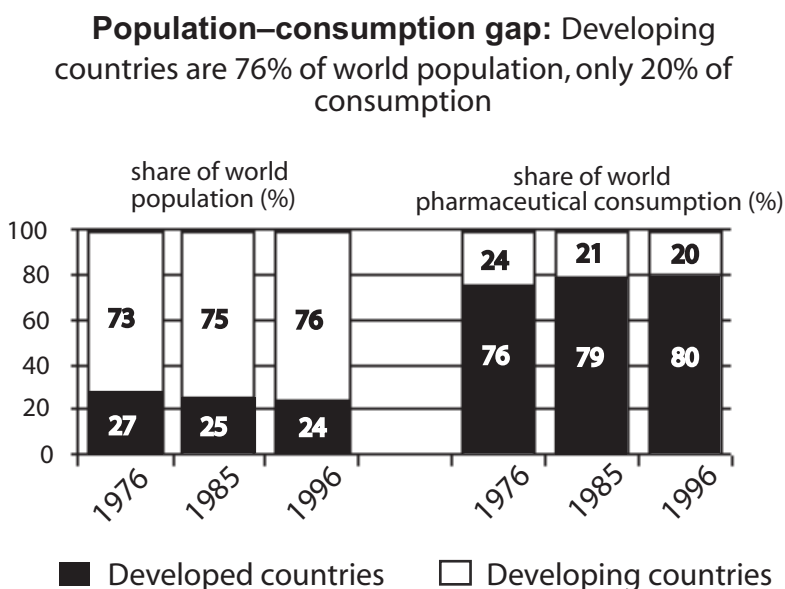
In addition, one can mention the 'population/consumption gap' (Fig. 1.2). The trend during the last quarter of the twentieth century saw no great change regarding the percentage share of the world's population – the developed world continued to decrease from 27% in 1976 to 24% in 1996 with corresponding increases in the developing world.



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**Figure 1.2. Population/Consumption Gap: Comparison Between Developed and Developing Countries**

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During the same period, the share of world pharmaceutical consumption showed a reverse trend – in the developed world consumption continued to increase, from 76% in 1976 to 80% in 1996, whereas the developing world continued to decrease correspondingly. Consequently, in 1996, despite accounting for 76% of the world’s population, the developing world only consumed approximately 20% of world pharmaceutical products. In other words, the developing world experienced a relative reduction in its share of pharmaceutical consumption when compared with 1976. To change the situation dramatically remains a challenge, especially in the light of the HIV/AIDS pandemic.

## Human Resource Gap

Apart from the financial inequalities, the quality of pharmaceutical care and development of pharmaceutical infrastructure is also dependent on the availability of qualified human resources. The number of qualified pharmacists per 100,000 population ranges from 0.1 in developing countries to 94 in developed countries.

The lack of pharmacists casts a heavy burden as it is not able to establish functioning regulatory systems or, in some cases, even elementary systems of quality control of medicines.

## Research and Development Gap

The targeting of research and development budgets towards the more sophisticated and lucrative markets in the developed world is to the obvious detriment of the developing world. Between 1975 and 1999, despite 1,393 new compounds being launched by the pharmaceutical industry, only 16 of them targeted tropical diseases and tuberculosis (Trouiller et al., 2002). The lack of drug research and development for ‘non-profitable’ diseases needs new policies and strategies. There is hope that the situation is slowly improving as there are numerous initiatives trying to fill the gap with joint actions from the public and private sector.

## Quality Gap

The medicines introduced must be safe, effective and of good quality. Unfortunately, many developing countries do not have the technical, financial, or human resources required for assuring that such standards are applied. WHO acknowledges the fact that the huge quality gap of pharmaceuticals still exists. On 24 May 1999, the 52nd World Health Assembly (WHA), by its resolution on Revised Drug Strategy [WHA52.19], expressed again its concern that *“poor quality pharmaceutical raw materials and finished products continue to move in international trade.”* They urged Member States *“to ensure that public health interests are paramount in pharmaceutical and health policies”* and *“to establish and enforce regulations that ensure good uniform standards of quality assurance for all pharmaceutical materials and products manufactured in, imported to, exported from, or in transit through their countries.”*

Despite the fact that WHO has urged the Member States in numerous WHA resolutions to take action, a recent WHO press release in November 2003 stated *inter alia*:

A recent WHO survey of the quality of antimalarials in seven African countries revealed that between 20% and 90% of the products failed quality testing. The antimalarials in question were chloroquine-based syrup and tablets, whose failure rate ranged from 23% to 38%; and sulphadoxine/pyrimethamine tablets, up to 90% of which were found to be below standard. The medicines were a mixture of locally produced and imported products (WHO, 2003c).

The data were based on a study that was published in 2003 (Maponga and Ondari, 2003). It should be noted for correctness that the dissolution studies showing the highest failure rate (up to 90%) used pharmacopoeial standards from developed countries rather than the pharmacopoeias from manufacturing developing countries, or respective specifications of the manufacturers.

The quality problem is not new. Earlier studies in the Amazonian region and Nigeria have attributed therapeutic failures at least in part to poor and variable potency of antimalarial drugs and suggested that quality problems are likely to be a factor in the selection for drug-resistant organisms (Petralanda, 1995; Taylor et al., 1995). Samples of chloroquine, amoxicillin, tetracycline, co-trimoxazole and ampicillin-cloxacillin taken in Nigeria and Thailand had lower than expected potencies, and six samples of chloroquine had no detectable active ingredients at all (Shakoor et al., 1997).

It seems that the situation is no better with medicines for another killer disease, tuberculosis. A six-country study on anti-tuberculosis drugs showed that 13% of single-drug and 21% fixed-dose combination drug samples were substandard (Laserson et al.). The manufacture of even generic quality medicines may not be an easy task and certainly requires skills. Changing manufacturing processes, variations in particle size and excipients, can all produce a marked change in bioavailability of rifampicin (Buniva et al., 1983; Fox, 1990). Different brands of rifampicin have been shown to have different bioavailabilities at the same dose (Garg et al., 1991). While bioavailability of antibiotic drugs may cause therapeutic failures and contribute to increasing bacterial resistance, many if not most manufacturers of these drugs in developing countries do not carry out any comparative bioequivalence studies of their products. This is confirmed by recent studies demonstrating therapeutic failures due to poor bioavailability, for example to rifampicin (Van Crevel et al., 2002).

Using poor quality starting materials from unreliable sources remains a big problem in many parts of the world. The most well known is the case of using diethylene glycol instead of glycerol in fever medicines which caused an epidemic of paediatric death due to renal failure in Haiti (O'Brien et al., 1998). This occurred between November 1995 and June 1996, when acute anuric renal failure was diagnosed in 86 children (aged 3 months–13 years) in Haiti; most (85%) children were aged less than or equal to 5 years old. In June 1996, a joint investigation was initiated by the Ministry of Health of Haiti, the University General Hospital in Port-au-Prince, the Pan American Health Organization/World Health Organization, the Caribbean Epidemiology Center, and the Center for Disease Control and Prevention (CDC) – more than 70 eventually died. To address the problems of poor quality starting materials WHO guidelines on *Good Trade and Distribution Practices for Pharmaceutical Starting Materials and WHO Pharmaceutical Starting Materials Certification Scheme (SMACS): Guidelines for Implementation* were finalized and published (WHO, 2004).

## **Regulatory Capacity Gap**

Among other factors, the regulatory capacity gap is clearly one that contributes to the devastating quality gap mentioned above. Huge differences exist in the regulatory environment and some countries may have just one single pharmacist in charge to fulfil all the functions of a Regulatory Authority. WHO recognizes that among its 192 Member States only approximately one-third has advanced regulatory systems, one-third has some regulatory systems and one-third has practically no functioning regulatory system in place.

However, very few comparative studies involving a number of Regulatory Authorities worldwide exist. The WHO multi-country study involving 10 drug Regulatory Authorities from different regions revealed that although the objectives are similar, the performance and resources of different Regulatory Agencies varies a lot. Overall, tendency is that resource-poor countries are less likely to control their pharmaceutical markets effectively, enjoy political support for the regulators, and have a properly resourced and functioning Regulatory Authority (Ratanwijitrasin and Wondemagegnehu, 2002).

This differing regulatory environment presents a challenge to policymakers and raises the question of how two-thirds of WHO's Member States can benefit from the emerging number of technically complex and demanding numerous ICH guidelines when their infrastructure is not compatible even for much more simple tasks. Many non-ICH countries at present are not able to implement the current WHO GMP or control even the generic drugs as suggested by the set of WHO norms and standards, mostly compiled into guidelines on registration of multisource (generic) drugs (WHO, 1999c).

When planning implementation of ICH products, careful consideration should be given to ensure that public health interests are paramount (WHO, 2002b). Country situations and needs are different at different stages of development. In all countries, drug regulation and drug regulators have an important role to play in protecting public health. The main responsibility of drug regulation is to safeguard the availability of good quality, safe and effective pharmaceuticals to all citizens. In order to assist countries in the quality assurance and safety of drugs, WHO continues to establish and develop clear, practical norms and standards, mostly for generic drugs that are affordable to the majority of the world's population.

Pharmaceutical regulatory harmonization facilitates the availability of safe, effective and good quality pharmaceuticals. WHO supports harmonization on national, regional, inter-regional and international levels. International consensus on quality, safety and efficacy standards can accelerate the introduction of new medicines and increase availability of generic medicines through fair competition, thereby lowering prices.

## WHO'S RESPONSE TO PHARMACEUTICAL GAPS: WHO MEDICINES STRATEGY

What is WHO doing in order to reduce the numerous gaps that exist in the area of pharmaceuticals? WHO established its '*Medicines Strategy*' for 2000–2003 (WHO, 2000) in order to reduce gaps. During these years, WHO focused on four priorities within its medicine strategy:

- Promoting access to essential drugs for priority health problems (e.g., tuberculosis, childhood diseases, HIV/AIDS) and by targeting this priority towards the poor and vulnerable populations
- Encouraging the quality and safety of all medicines by the creation and maintenance of global guidelines and standards and supporting effective drug regulation and quality assurance programmes
- Advocating the importance of rational use of medicines by health professionals and by households, and
- Supporting the introduction of national drug policies that are integrated into national health policies and systems and which emphasises implementation and monitoring

The very concise formulation of strategy objectives does not give a comprehensive overview of all WHO activities in the area of quality and safety of medicines. More information is found on the Essential Drugs and Medicines Policy Department website (<http://www.who.int/medicines/>).

The world is changing and the strategy is being updated to address these needs. The new *Medicines Strategy for 2004–2007* will be issued shortly and can be easily accessed through the website, where it will replace the working draft (WHO, 2003d). The basic objectives remain the same, i.e., promoting the right policy, access, quality and safety and rational use of medicines. Quality related issues remain high on WHO's agenda for the forthcoming four years.

## INTERNATIONAL CONFERENCE OF DRUG REGULATORY AUTHORITIES (ICDRA)

WHO has convened the International Conference of Drug Regulatory Authorities (ICDRA) every two years since 1980 to build collaboration between regulators globally, to promote harmonization and exchange of information, and seek common

approaches to problems facing all drug Regulatory Authorities (ICDRA, 2003). ICDRA is a unique forum for regulators from both the developing and developed world to exchange information.

The 9th ICDRA was held in April 1999 in Berlin, Germany, with the participation of 90 countries and a total of 280 senior regulatory officials. The 10th ICDRA was held in June 2002 in Hong Kong, China, with the participation of more than 100 countries (WHO, 2002c). Among others, the following recommendations were made in Hong Kong:

- WHO should continue its efforts in strengthening international guidelines for registration of generic drugs
- In the light of the wide range of regulatory environments, WHO should support non-ICH Member States and regional harmonization initiatives by evaluating the usefulness, feasibility and impact of implementing ICH guidelines
- Countries should implement programmes aimed at assuring the availability, accessibility, quality and rational use of essential drugs
- The pharmaceutical industry should pay particular attention to GMP and quality issues in relation to the production of antimicrobials as well as to the labelling of their products
- In collaboration with Members States, WHO should continue to focus on activities related to good trade and distribution practices for starting materials to assure the use of high quality materials
- WHO should continue its prequalification project for procurement of medicines for priority diseases
- Governments should acknowledge the problem of counterfeit drugs by developing national policies and providing a comprehensive legal framework to regulate trading of counterfeit drugs as a criminal offence

The ICDRA recommendations serve as a guide to WHO. Work must continue among the numerous members of ICDRA on strengthening progress in the area of assuring quality through harmonization of technical standards, since this varies from one region to another and from one country to another. The 11th ICDRA took place in Madrid, Spain, in February 2004 with an emphasis on what regulators can do more to facilitate access to the good quality essential medicines including fighting substandard and counterfeit drugs.

## **REGIONAL HARMONIZATION INITIATIVES: SETTING PRIORITIES**

Harmonization of technical requirements for the registration of medicines can contribute to public health by improving access to safe, effective and good quality pharmaceutical products. It can also facilitate developing a fair and transparent regulatory processes, improve international collaboration, reduce duplication of work by different Regulatory Agencies and facilitate trade and competition.

The harmonization initiatives, whether regional or sub-regional, are ongoing in all WHO regions. The major focus of many of those initiatives is to first harmonize basic regulatory requirements for generic drugs. In contrast, the ICH has been focusing on establishing harmonized requirements to evaluate quality, safety and efficacy of new innovative drugs, thus avoiding the necessity to duplicate many time-consuming and expensive test procedures. As a result, the time spent on regulatory approval of new drugs has been shortening and marketing of these products takes place internationally with minimal delay for the patients. By ICH-6 in 2003 the ICH regions have largely harmonized regulatory requirements for quality, safety and efficacy of new drugs, including a Common Technical Document (CTD). However, new technologies necessitate new regulatory approaches and work on new selected topics and pharmacovigilance is continuing.

In non-ICH countries, WHO/EURO actively supported the establishment of the Collaboration Agreement of Drug Regulatory Authorities in European Union-Associated Countries (CADREAC) collaboration which has made rapid progress since its first Annual Meeting in Sofia, Bulgaria, in 1997. Ten CADREAC countries have largely finalized their regulatory harmonization and are expected to join the European Union in 2004 (WHO, 2002d). Although very specific, it is currently second to the successful ICH harmonization initiative. It seems important for the progress of harmonization that participating countries have high political commitment and the same or similar socio-economic level of development.

The Pan-American Network for Drug Regulatory Harmonization (PANDRH), with the support from the Pan-American Health Organization (PAHO), has made a lot of progress since its first Steering Committee meeting in 2000 in Puerto Rico. The other initiatives progressing are the ASEAN Pharmaceutical Harmonization and harmonization among Southern African Development Community (SADC) countries. Both of these initiatives have been supported by WHO. Many of the non-ICH harmonization initiatives emphasize the importance of training of regulators as an important vehicle to drive harmonization forward, especially under circumstances where the level of economic development of participating countries varies a great deal.

## REMAINING CHALLENGES

The huge gaps in regulatory capacity are hindering effective drug regulation and harmonization. Limited resources and lack of political pressure will have slowed down the progress. The regulatory approval of generic drugs which are more affordable for patients still remains mainly unharmonized, paradoxically more in the countries where the healthcare systems have to rely heavily on generic drugs. Regulatory assessment of products by national authorities with limited capacities, especially in the case of new drugs, often gives limited, if any, added value to the work already done by other Regulatory Authorities. The value of mutual recognition is underestimated due to the lack of trust in the scientific assessments carried out by other Regulatory Agencies. There is also a tendency to adopt sophisticated technical requirements while basic measures to protect public health and ensure the quality (e.g., Good Manufacturing Practice and supply chain inspection) of medicines have not yet been implemented.

Global harmonization is ideal, but we have to be realistic in terms of available resources and take a step-by-step approach by setting clear priorities. There is no place for extremely sophisticated technical requirements when simple quality assurance measures to ensure protection of public health have not yet been implemented. Effective pharmaceutical inspectorates, together with the implementation of Good Manufacturing Practices and elementary requirements for product quality specifications, are first essential to ensure that poor quality and counterfeit drugs are not allowed to enter national territories. Updated legal systems, functional Drug Regulatory Authorities and quality control laboratories are all prerequisites before any harmonization activities can be developed.

In many countries essential generic drugs are those that are affordable to the majority of populations, but their quality often varies. The quality of drugs, and therefore their effectiveness and safety, are less certain – especially for the poorest populations, who are attracted by lower-priced drugs sold outside regulated distribution channels.

WHO has the mandate to establish global standards and it has established a comprehensive set of norms and standards for ensuring the quality of generic drugs, but their implementation still needs greater national and regional efforts. It also needs significantly more resources to help those who have no resources to help themselves.

In order to reduce the existing quality and regulatory gaps, WHO supports capacity building and training of regulators by issuing norms and standards and guidance materials (see above). WHO creates norms and standards through its Expert Committee system and wide consultation with all Member States. The results of the Expert Committee on Specification for Pharmaceutical Preparations technical documents are published in the *Technical Report Series* (TRS) publications; the latest was published in 2004 (WHO, 2004).



The lack of the latest norms and standards for quality of medicines is less of a problem than implementation in many parts of the world. WHO is actively creating training tools (e.g., validated GMP training modules on CD ROM) and is organizing training seminars and workshops. During the last few years an impressive number of government officials and industry representatives have been trained in many middle- and low-income countries covering almost all WHO regions (Morimoto et al., 2003). Furthermore, it facilitates the exchange of information through *WHO Drug Information*, *WHO Pharmaceutical Newsletter*, *Rapid Alerts* and through the Internet with its website where, for example, many guidelines and International Non-proprietary Name (INN) databases can be found (<http://www/who.int/medicines>).

## CONCLUSIONS

WHO is working, with the help of numerous partners, on reducing pharmaceutical quality gaps around the world. It is assisting individual countries as well as regional harmonization initiatives by providing technical assistance and advice, as well as on priority-setting. The prime challenge for non-ICH countries is to decide which direction to take to get the best possible protection of public health with the limited resources available. When resources are scarce, recognition of scientific expertise made by Regulatory Agencies with more available resources remains an option for consideration, especially in those cases of complicated new drugs and technologies. *The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* (WHO, 1988) can serve as a valuable tool when this option is chosen. WHO has always underlined that equal standards of quality should be used for manufacturing drugs for domestic use and export.

In conclusion, the ultimate goal of the activities of the international community as a whole in the area of medicines quality should be to improve access to quality drugs to all sectors of the global population. Much more cooperation and joint efforts are needed to join the attempts of all major stakeholders to reduce the aforementioned global pharmaceutical quality and regulatory gaps. The world community has a challenge to change the unfortunate reality of today, in which for many patients in less favoured countries there is a lack of access to essential life-saving drugs. “*Poor quality drugs for poor people*” should not be accepted any longer. It is our collective task to cure the global disequilibrium of quality from a medicines perspective.

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