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Review

Regulatory framework for access to safe, effective quality medicines

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Medicines of uncertain quality, safety and efficacy can be worse than no treatment at all. It is the responsibility of national medicines regulatory authorities to protect patients from harm. Yet, there are great disparities in regulatory capacity globally, preventing large populations from accessing the benefits of advances in the pharmaceutical field. This article describes the main regulatory functions and how they are applied to assure the quality, safety and efficacy of different types of medicines in different environments. It gives examples of initiatives that have increased access to good quality medicines worldwide and – more importantly – are laying the groundwork for collaborative approaches aiming to ensure that pharmaceutical products meet the same, stringent quality standards in all parts of the world.

Introduction: regulation of medicines

Why regulate medicines?

Drugs are not ordinary consumer products as they directly affect the lives of people who take them. They are complex products and their quality cannot be seen by looking at them. They can restore people's health, but all medicines can have adverse effects. This means that consumers need guidance on how to use medicines. Even health-care professionals need special training and access to specialized information to safely deal with medicines at all stages of their development, production, distribution and dispensing.

Medicines that do not meet their intended specifications can cause serious harm: they can worsen a disease process, encourage development of causative organisms or processes that are resistant to medicines, and they can sometimes lead to death. This in turn will undermine confidence in health-care professionals, pharmaceutical manufacturers, distributors and health systems. Money spent on ineffective, unsafe and poor-quality medicines is not only wasted, it will cause damage that can result in human suffering and huge additional costs.

Governments have the responsibility to guide and protect their citizens in the areas where the citizens cannot protect themselves. Thus, Governments need to establish strong national medicines regulatory authorities (NMRAs) to ensure that the manufacture, trade and use of medicines are regulated effectively. In broad terms the mission of an NMRA is to protect and promote public health. Medicines regulation requires sound scientific knowledge and skills in the medical, pharmaceutical, biological, chemical and other related fields – all applied within a legal framework to serve the public good.

Implementing equitable medicines policies and strategies within the political and economic context of a country or region is a challenging task. In 1975, the World Health Assembly requested the World Health Organization (WHO) to assist Member States in formulating national medicines policies. This led to the concept of essential medicines, defined as those products that satisfy the priority health-care needs of the population. The WHO proposes model lists of essential medicines for adults and children, for adaptation by countries in-line with their own public health needs and priorities [1]. The first WHO essential medicines list, published in 1977, had 205 items – a surprisingly low number compared with the thousands of different medicines, some more useful than others, that were circulating in countries. By prioritizing measures to ensure that essential medicines are of good quality and available at a reasonable cost, countries can optimize

the public health impact of their regulatory resources. Over the years the list increased in size as additional medicines were included. The first antiretrovirals (ARVs) for prevention of mother-to-child transmission of HIV infection were included on the 11th edition of the list. In 2002 the WHO Board adopted a new, evidence-based process for revising the list, bringing about a breakthrough as several patented ARVs were included on the 12th essential medicines list.

What does medicines regulation entail?

Medicines regulation includes several related activities all aimed at promoting and protecting public health. These activities vary from country to country in scope and implementation, but generally include the functions listed in Table 1.

What makes regulatory systems effective?

Medicines regulation involves various stakeholders: manufacturers, importers, exporters, e-commerce companies, consumers, health-care professionals, researchers and government institutions. These stakeholders have vastly different economic, social and political motives. Given the resulting real and potential conflicts of interest, medicines regulation can only be effective if its decisions are independent and strictly science-based, ensuring that medicines are safe, effective and of good quality. The WHO experience in providing regulatory support points to some success factors that enable effective regulation in a country. Contextual factors include: political will and commitment to Good Governance in regulation [2]; adequate availability of medicines to avoid smuggling and illegal use; strong public support for drug regulation; effective cooperation across national authorities (for example, medicine regulators, customs and police); and sufficient qualified and experienced professionals. Institutional factors include: a clear mission statement; adequate medicines legislation and regulation; appropriate organizational structure and facilities; clearly defined roles and responsibilities; adequate and sustainable financial resources to retain and develop staff; relevant guidelines and procedures; and an effective internal quality assurance system.

There are few in-depth comparative studies of national regulatory systems. The WHO assesses NMRAs to determine gaps as a basis for institutional development plans to address these gaps. Some insights from this work have been documented [3,4], indicating that regulatory capacity around the world varies greatly, with a considerable number of NMRAs falling short of assuring the implementation of the minimum functions shown in Table 1.

Technical standards for medicines regulation

Assessing innovative medicines: ICH guidelines and the CTD document

Different types of medicines need to be assessed in different ways. Innovative medicines (originator products) are new medicines that have not been used in humans before and often contain new active ingredients. These medicines are often protected by patents and may be subject to data exclusivity. Under a data exclusivity regime, the respective regulatory authorities would be prevented for a certain number of years from relying on the data (safety and efficacy) submitted in the application for the originator product, in order to approve later generic versions of the product [5].

Today, most originator medicines are first approved by well-resourced regulatory authorities according to the harmonized requirements of the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use* (ICH). This forum brings together regulatory authorities and the pharmaceutical industry of the European Union (EU), USA and Japan to make new products available to patients more quickly while

Table 1. Medicines regulatory functions

NMRA functions	At a minimum, NMRAs should:
License the manufacture, import, export, distribution, promotion and advertising of medicines	Ensure that all activities and premises comply with Good Manufacturing Practices and other good practices
Issue marketing authorizations for products (drug registration)	Before medicines are marketed, assess their safety, efficacy and quality
Inspect manufacturers, importers, wholesalers and dispensers of medicines	Control the manufacturing units and supply chain including informal market and e-commerce to prevent illegal trade of medicines
Control and monitor the quality and safety of medicines on the market, collect and analyse reports on adverse events	Prevent harmful, substandard and counterfeit medicines from reaching the public
Control promotion and advertising of medicines	Prevent misleading information from reaching the public and health professionals
Provide independent information on medicines to professionals and the public	Prevent irrational use of medicines

Adapted with permission from [24]. NMRAs, national medicines regulatory authorities.

protecting public health. The ICH develops and maintains a framework of technical topics [6] that serve as a reference for many aspects of medicines regulation with the focus on new drugs (Table 2).

ICH guidelines are not mandatory *per se*. The strength of the ICH process lies in the commitment for implementation by the ICH members. For example, in the EU all ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) for endorsement once they have reached a certain maturity in the consultation process, denoted by 'Steps'. The CHMP, in consultation with the European Commission, decides on the duration for consultation of up to 6 months with interested parties. The EMA publishes and distributes the Step 2 guidelines for comment. At Step 4 the CHMP endorses the guidelines and determines a time frame for implementation that is usually around 6 months. The guidelines are then published by the European Commission in the Rules Governing Medicinal Products in the EU.

A second important tool for regulatory harmonization developed by ICH is the harmonized format for applications for marketing authorization called the Common Technical Document (CTD). It consists of five modules for submission of product data according to ICH technical requirements: module 1, country-specific administrative data and prescribing information (not part of the harmonized CTD); module 2, summaries of sections as described in ICH guidelines (how the application is organized [M4], quality [M4Q], safety [M4S] and efficacy [M4E]); module 3, quality; module 4, non-clinical study reports; and module 5, clinical study reports.

The full compiled content of a submission in CTD format takes into consideration technical requirements of more than 60 ICH guidelines.

ICH formats and guidelines are also implemented in ICH-associated countries such as Canada and Switzerland, and are fully or partially used in countries that are not part of the ICH. Registration of new medicines by less well-resourced regulatory agencies is often based on first approval either by the US Food and Drug Administration (USFDA) or by the EMA. Many ICH guidelines, especially those concerning preclinical and clinical research, are of interest to the research community and can also serve as educational tools. Directly and indirectly, ICH guidelines thus have a major impact worldwide.

As the vast majority of all new medicines are developed and approved in the ICH regions or associated countries, the technical requirements for the safety, efficacy and quality of new medicines are determined largely by ICH technical guidelines.

Assessing multisource or generic medicines

Multisource or generic medicines are 'copy' versions of an innovator medicine. Generic medicines can be marketed legally when patent and other exclusivity rights of the originator's product expire, where relevant patents do not exist or where licenses (voluntary or compulsory) are available. Generic medicines have an important role to play in public health as they are usually less expensive and therefore more affordable than patent-protected medicines because of the competition between generic products.

Generic medicines are designed to work the same way as originator products, for which the safety and efficacy has been demonstrated in clinical trials. Instead of repeating these trials, the key assessment of a generic medicine is its therapeutic interchangeability with the originator product. If a generic drug is therapeutically interchangeable with the originator product, it can then be assumed to be equally safe and effective.

Table 2. The ICH framework of standards

Area	Topics	Examples of guidelines
Q – Quality	Chemical and pharmaceutical quality assurance	Q1 stability testing
		Q3 impurity testing
S – Safety	*In vitro* and *in vivo* preclinical studies	S1 carcinogenicity testing
		S2 genotoxicity testing
E – Efficacy	Clinical studies in human subjects	E2 clinical safety data management
		E4 dose–response studies in carcinogenicity testing
		E6 good clinical practices
M – Multidisciplinary	Cross-cutting topics	M1 medical terminology
		M2 electronic standards for transmission of regulatory information
		M3 timing of preclinical studies in relation to clinical trials
		M4 the common technical document
		M5 data elements and standards for drug dictionaries

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines available from [6].

Regulatory criteria for assessment of generic medicines have thus been agreed upon, requiring that a generic medicine must: contain the same active ingredient(s) as the innovator drug; be identical in strength, dosage form and route of administration; have the same indications for use; be bioequivalent, that is, release active ingredient(s) into the body at the same rate as the originator product; meet the same batch requirements for identity, strength, purity and quality; and be manufactured under the same strict standards of Good Manufacturing Practice (GMP) required for innovator products.

The WHO has developed a comprehensive set of guidelines for assessment of generic medicines summarized in a guidance text [7]. Its principles are in-line with stringent international regulatory standards such as the ICH requirements. These guidelines and many others on all aspects of medicines quality assurance are developed in a global consultation process through the WHO Expert Committee on Specifications for Pharmaceutical Preparations and are available on the WHO website [8].

As the vast majority of innovative medicines are initially approved in the ICH region, regulatory authorities in less well-resourced settings will typically use the 'generic' approach to assess additional marketing applications in their own countries, relying on the clinical safety and efficacy assessment done on the originator product in a stringent regulatory environment.

However, for some types of medicines there is no originator product approved in a stringent regulatory environment. In such cases, specific workable regulatory solutions need to be found for assessment and approval. The above-mentioned WHO consultative process has succeeded in reaching consensus in such situations. For instance, fixed-dose combination (FDC) products containing ARV medicines were in urgent demand at the turn of the century to combat the HIV pandemic. While stringently assessed originator products existed for the single-ingredient products, FDCs were only produced by companies based in countries with little regulatory experience on these products. In 2004, the leading regulators of the world agreed on the principle, proposed by the WHO, that if several separate medicines have successfully been used in combination therapy there is no need for additional clinical trials for an FDC of the same medicines in the same dosages. Instead, it must be shown that the combination tablet achieves the same serum levels of each active ingredient as did the originator products when given separately. This approach enabled regulatory assessment to proceed, bringing these needed products to market at affordable prices and saving countless lives.

Another example involves artemisinin-based combination therapies (ACTs). These are currently the only remaining effective treatment for malaria in most endemic areas of the world. Artemisinin is derived from a plant traditionally used in China to treat malaria, and few ACTs are approved in a stringent regulatory environment, where malaria is typically not endemic. Through its consultative process, the WHO developed specific guidance on the assessment of these products and applied it to prequalify medicines for use by United Nations (UN) agencies. This enabled donors to make an unprecedented switch away from outdated ineffective therapies and replace them with safe and effective ACTs provided at sustainable prices.

These examples illustrate the fine balance that effective regulation needs to achieve in order to ensure the quality, safety and efficacy of medicines while enabling their prompt access to patients in need.

The role of pharmacopoeial standards

In the pharmaceutical sense, a pharmacopoeia – from the Greek *pharmako-poios* or 'drug-maker' – is an official publication that lays down quality standards for medicinal products. They can be national like the United States Pharmacopeia or the British Pharmacopoeia, or regional like the European Pharmacopoeia. The WHO maintains The International Pharmacopoeia through the Expert Committee for Specifications for Pharmaceutical Preparations and provides it free of charge on the WHO website [9].

A pharmacopoeia contains a number of general texts, as well as monographs for individual drug substances and finished dosage forms. They describe a set of tests that will confirm the identity and purity of the substance or product, the amount of active substance and related substances (impurities) contained in it, and other characteristics such as its dissolution or disintegration properties. A pharmacopoeia thus enables independent quality control testing of drug substances and finished products to verify whether they conform to their technical specifications. Pharmacopoeial monographs are also useful for generic manufacturers that choose not to elaborate their own specifications but rather to develop a product such that it meets the published requirements both for the active ingredient and the finished dosage form.

Quality control testing according to pharmacopoeial standards has certain limitations. For example, as the tests are often based on the specifications of the manufacturer that developed the innovator product, they may be designed to detect certain expected impurities based on a given route of synthesis, but they may miss many other potentially harmful impurities if a different route of synthesis is used or accidental contamination occurs. This is why stringent regulatory authorities will not approve products based on pharmacopoeial testing alone. In fact, pre-marketing quality

control testing is being used less and less, and more emphasis is placed on surveillance after the product is put on the market to ensure that each batch meets the approved specifications.

At the same time, there has been a shift away from quality control of finished dosage forms towards the control of all processes and procedures involved in the manufacture of active pharmaceutical ingredients (APIs) and finished dosage forms. This control is executed using thorough scientific assessment of data and inspecting the sites involved in manufacture, clinical and laboratory testing. The objective of today's regulatory approval is to ensure that the manufacturer has built quality into the product from start to end. Compliance with GMP for APIs and finished dosage forms as recommended by the WHO and laid down in national laws is vital. GMP is applicable to the entire manufacturing chain of a product, whether it is an innovator or a generic product.

From this, it becomes clear that effective regulation goes far beyond quality control testing. Although pharmacopoeial standards have a use in GMP inspections and in the assessment of quality specifications, bioequivalence data, stability data and labelling information provided by the manufacturer, testing according to pharmacopoeial methods is not a replacement for these detailed regulatory measures.

The current global regulatory environment

National regulatory bodies: roles and challenges

NMRAs have the legal mandate to regulate medicines within their jurisdiction. Although globalization of pharmaceutical manufacturing and trade, and advancing technologies are all potentially helping to increase access to new therapies and affordable products, they are making it increasingly challenging for NMRAs worldwide to perform their regulatory tasks. Today, no NMRA can function in isolation any more. The ICH was created because its members realized that without effective collaboration and harmonization of approaches they cannot fulfil their mandate – to protect the health of their citizens. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) were created to provide international instruments for collaboration in the field of GMP between national pharmaceutical inspection authorities, which provide together an active and constructive co-operation network.

The wide recognition of the need for collaboration has led to a number of other initiatives, focusing at first on harmonization and convergence of technical standards and regulatory guidance. Examples include the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization initiative, the African Medicines Regulatory Harmonization (AMRH) initiative, the International Regulatory Cooperation for Herbal Medicines (IRCH), the International Generic Drug Regulators Pilot (IGDRP) project and the Pan American Network for Drug Regulatory Harmonization (PANDRH).

The WHO Prequalification Programme

In the absence of effective regulatory systems in many of the WHO Member States, the WHO Prequalification Programme aims to ensure that health products, including medicines, vaccines and diagnostics, meet global standards of quality such that they are suitable for procurement by UN agencies and other donors [10]. Prequalification of vaccines started in 1987, and prequalified vaccines are used today to immunize 65% of infants worldwide. The Prequalification of Medicines Programme was established in 2001 to address two main challenges: insufficient in-country capacity to assess medicines quality and the limited choice of affordable treatments for diseases affecting large populations. The WHO prequalification of diagnostic products has been added in recent years, focusing mainly on HIV *in vitro* diagnostics.

Today, the WHO has prequalified over 350 finished pharmaceutical products, of which about 200 are for treatment of HIV/AIDS. In the past 13 years the WHO Prequalification Programme was essential in the efforts to scale-up treatment of people living with HIV (PLHIV). It is estimated that of the 9.7 million PLHIV in middle- and low-income countries receiving treatment for HIV as of December 2012 [11], four-fifths were taking WHO-prequalified products [12]. Since 2006, Indian-produced generic ARVs have accounted for more than 80% of the donor-funded procurement [13] purchased in-line with quality policies that require that products meet the standards of the WHO and stringent regulatory authorities. The Prequalification Programme has also expanded its activities to APIs and quality control laboratories.

Although prequalification is based on stringent quality standards, it is nevertheless within the reach of manufacturers from all parts of the world, including those with limited experience and capacity. Technical assistance is provided to companies producing medicines with a high public health value.

The prequalification process is similar to a regulatory assessment. The manufacturer is required to submit product data in CTD format, which will be evaluated by a pool of regulatory assessors from diverse regulatory environments. Evaluation is based on the comprehensive set of guidelines developed by the WHO Expert Committee. Secondly, GMP inspections of the manufacturing sites of the finished product and the API as well as the clinical trial site will be conducted on a risk basis, meaning that the inspection can be waived for

sites considered to be low risk – for example, those successfully inspected previously by the WHO or another organization with stringent standards. A fast-track procedure is in place for prequalification of products approved by stringent regulatory authorities.

Comprehensive information on the process and outcomes of medicines prequalification is updated daily on the Programme's website [14]. Interested companies can identify potential candidate products from the WHO expression of interest list, and weigh the expected investments needed for prequalification against the expected returns given the market perspectives for the product [15]. The actual prequalification process can take anywhere from a few weeks to several years, depending on the capacity and experience of the manufacturer and the quality of the initial submission. Additional data will be requested and additional inspections conducted until all the required standards are met.

Once a product is prequalified, the manufacturer can expect a number of benefits: access to donor-funded markets, substantial tender volumes, access to regulatory fast-track mechanisms, an improved corporate image, and new or increased capacity to complete stringent regulatory processes successfully.

In analogy to accelerated assessment mechanisms recently introduced by USFDA and EMA to accelerate access to needed medicines, a risk-based mechanism exists to identify medicines meeting minimum quality standards for temporary procurement by international organizations until prequalified medicines become available. The Expert Review Panel (ERP), hosted by the WHO, provides risk-based assessments of needed products that have not yet achieved WHO prequalification or stringent regulatory approval. To qualify for ERP review a medicine must be included on the invitation list for expressions of interest, and must be produced at a site that has passed a stringent GMP inspection. The ERP classifies medicines into risk categories according to transparent, publicly available criteria [16] with the aim to help international organizations make informed procurement decisions. An expanded mechanism has been proposed for exceptional cases where insufficient data are available to support a positive opinion for an urgently needed product [17].

Capacity-building has been one of the core elements of the Prequalification Programme since the very beginning. Each year a large number of activities are organized. In 2012 the programme conducted 31 technical assistance missions and organized or co-organized 27 training workshops reaching more than 1,000 manufacturer representatives, more than 300 regulators and 150 other stakeholders in all six WHO regions.

Perhaps even more importantly, national regulators are involved in all major prequalification activities: assessing product dossiers and inspecting manufacturing sites, clinical trial sites and quality control laboratories. In addition, four consecutive rotational fellowships are offered each year to interested regulators from developing countries. To date, more than 30 regulators have completed a 3-month rotation at the Prequalification Programme in Geneva – a unique arrangement within the WHO. This hands-on experience builds capacity for pharmaceutical quality monitoring and joint problem-solving.

The long-term impact of WHO prequalification thus goes far beyond procurement. The Programme has raised the standard for quality assurance of medicines. Its standards are recognized and promoted by others, helping to expand quality medicines production. For example Medicines Patent Pool licenses – that offer the possibility of generic production even when a patent exists – require that producers adhere to the WHO prequalification rules. The capacity-building effect for producers and regulators has paved the way for a number of collaborative initiatives, some of which are described in *Changing regulatory environment in WHO African region: examples of new initiatives and increasing collaboration*.

Access to HIV treatment: a case study

The WHO Prequalification Programme has been essential in the efforts to scale-up treatment for PLHIV. In 2000, only one in a thousand PLHIV in Africa had access to ARV treatment (ART). ART was available in high-income countries and had changed HIV and AIDS from a death sentence into a manageable chronic disease. But the ARVs were available only from originator companies, who controlled the patents. They produced small quantities costing 10,000–15,000 USD per person per year, unaffordable for most PLHIV in middle- and lower-income countries.

When in early 2000 the world turned its long overdue attention to the HIV and AIDS crisis in the middle- and lower-income countries it had to find a solution for the high cost of ARVs. Producers of generic versions of ARVs were mostly from India and offered ARVs at lower prices. Indian firms were the first to produce an FDC of a WHO-recommended first-line combination. GlaxoSmithKline did offer a combination of its compounds abacavir, lamivudine and zidovudine in one pill in early 2000, but this was not a WHO-recommended first-line regimen. The Indian firms could do so because there were no patent barriers in India to putting three compounds of different originator companies together in one pill. The price of the first generic triple combination by Cipla in 2001 was 350 USD and soon dropped to less than 140 USD per person per year [18].

However, controversies broke out over patents on ARVs following the introduction of new global rules

on intellectual property by the World Trade Organization in 1995, which had introduced tighter patent requirements for medicines [19]. These patents largely restricted organizations such as UNICEF or Médecins sans Frontières (MSF) from distributing generic ARVs made in India.

The ARVs, including the new FDCs produced by generic companies in India, needed quality assurance. This problem demanded a quick solution as buying the costly originator medicines was not an option. The WHO-proposed approach for assessing generic ARV FDCs, described earlier in this paper, was used to determine whether the inexpensive and more convenient products from generic suppliers had the same efficacy and safety profile as the originator products.

In 2002, the WHO published its first list of 41 prequalified HIV-related medicines. This opened up a supply of quality-assured low-cost generic ARVs for global procurement and helped to establish the market for generic ARVs. The Global Fund to fight AIDS, TB and Malaria (Global Fund), created in 2002, subsequently adopted a policy that restricts use of the Fund's immense purchasing power to products approved by stringent regulatory authorities or prequalified by the WHO. This became the norm for global health funders and as a result the publicly funded market for medicines for HIV, tuberculosis and malaria of unknown quality shrank quickly.

On 1 December 2003, the WHO and UNAIDS declared the lack of HIV/AIDS treatment to be a global public health emergency and launched the '3 by 5' campaign to get three million people on ART by 2005 [20]. The political momentum of the campaign, combined with new funding from governments, the Global Fund, the President's Emergency Fund for AIDS Relief (PEPFAR), and later from UNITAID, allowed countries to begin purchasing HIV medicines in large volumes at prices that soon decreased drastically. The triple FDCs, produced only by generic companies, came to symbolize the great savings that generics could achieve. The WHO prequalification of Cipla's first generic FDC of three-in-one ARV in 2003, a ground-breaking move, brought an important innovation to resource-poor countries.

FDC ARVs were an important advance in HIV treatment and positive outcomes were reported from resource-poor settings [21], where the Cipla 'one pill twice a day' regimen (Triomune) would help increase adherence to treatment, reduce the risk of emerging resistance, and simplify the supply chain.

The WHO Prequalification Programme is strict and does not hesitate to delist products when the applicant's dossiers are not up to standard. This happened for the first time in 2004 when the WHO delisted generic ARVs because of irregularities at the clinical study sites where bioequivalence was established, signalling to the industry that the Prequalification Programme had teeth and that from now on they had to play by the rules if they wanted to have a share of the rapidly growing ARV market [22].

In 2004 the US government established its own process, called the USFDA's Tentative Approval Mechanism, to approve ARVs for procurement using PEPFAR funding. While initially this mechanism was seen as a direct competitor to the WHO Prequalification Programme, both organizations today collaborate.

Changing regulatory environment in WHO African region: examples of new initiatives and increasing collaboration

The leadership of the African Union is committed to ensuring access to essential medicines for all African countries. In cooperation with development partners the Pharmaceutical Manufacturing Plan for Africa was launched in 2007 [23]. Clearly this ambitious plan required strengthening national regulatory authorities in the region.

Setting up the AMRH initiative took several years. In response to a request from Member States at the 2008 *International Conference of Drug Regulatory Authorities* (ICDRA) – a WHO-organized forum bringing together regulators from around 100 countries – the WHO initiated consultations that led to the formation of a Consortium involving the Pan-African Parliament (PAP), the New Partnership for Africa's Development (NEPAD), the Bill & Melinda Gates Foundation, the UK Department for International Development (DFID), the Clinton Health Access Initiative (CHAI) of the William J Clinton Foundation, the World Bank, UNAIDS and the WHO. In 2009, regional Economic Communities were invited to submit project proposals. A trust fund was established, and the administration agreement between the World Bank and the Bill & Melinda Gates Foundation was signed in 2011. The first grant was awarded to the East African Community (EAC), and the EAC Medicines Registration Harmonization was launched in 2012, marking the official beginning of the implementation phase of the AMRH programme across Africa.

The WHO did not wait for the official start of AMRH to organize collaborative initiatives. In 2010 it conducted a joint assessment exercise with EAC assessors. Dossiers for two products were submitted at the same time to the WHO Prequalification Programme and to EAC countries and evaluated during several joint sessions. One product became prequalified in August 2010 and was promptly registered in Uganda, Tanzania and Kenya. The other was prequalified in January 2011 and was registered in the countries within the usual timelines due to legal sample testing requirements. A second joint assessment project involving all five EAC countries started in July 2013 with five products. It is anticipated that based on these experiences EAC countries can set

up a more effective regulatory system in the region based on cooperation, work-sharing and mutual trust.

Another WHO initiative is the collaborative registration of WHO-prequalified products, introduced in 2012. Interested manufacturers of prequalified products can request for the WHO to share its detailed prequalification assessment information confidentially with participating NMRAs. If the NMRA agrees to use the collaborative procedure for a specific submission, it undertakes to issue its independent decision within 90 days of receiving access to the shared information. By January 2014, 16 national submissions were approved in countries, 14 of them within the expected short timelines. This constitutes a vast improvement on sometimes notoriously long registration times. More importantly, the initiative enables participating NMRAs to leverage work already done by the WHO prequalification team to control products more efficiently before and after registration in their countries.

Conclusions

Access to safe, effective medicines of good quality, meeting current international regulatory standards can only be achieved through fully functional regulatory systems with adequate capacity to undertake rigorous scientific assessment of these products.

Many regulatory authorities that do not have such systems adopt and adapt international (such as the WHO or the ICH) standards or those of 'reference regulators' chosen through some form of assessment or simply based on trust, and they rely on such reference regulators in their decision-making, especially where new and complex medicines are concerned.

For some priority medicines in countries lacking an effective medicines regulation system, this function is currently being fulfilled by the WHO Prequalification Programme. The collaborative approaches built into the Programme's activities have strengthened regulatory capacity in many NMRAs, paving the way for the uptake of new initiatives. Ambitious projects are under way, such as the African Medicines Registration Harmonization Initiative with current focus on EAC countries and soon to be expanded to other regional economic blocks in the region. Despite some daunting challenges, this presents good opportunities for reshaping the regulatory systems in Africa.

In the long-term it is envisaged that all national regulators and their collaborative networks are gradually enabled to assume their regulatory functions to assure medicines quality to current international standards. Given the fast pace of global development and change, pursuing this vision needs continued commitment from concerned governments and international partners.

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