

Effective medicines regulation: ensuring safety, efficacy and quality

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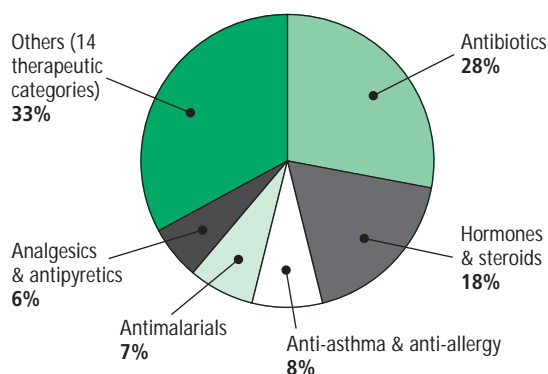
Currently about 20% of countries have well developed and operational medicines regulation. Of the rest approximately half have regulation of varying capacity and level of development, and 30% have either no or very limited medicines regulation. The reality is that many low-income countries cannot ensure the safety, efficacy and quality of medicines circulating on their markets. The problems of ineffective regulation transcend national borders and have global implications.

A recent WHO study provides one example of these problems, showing a high failure rate in quality control tests on chloroquine tablets in some sub-Saharan African countries (Figure 1). Only 58% of the medicines tested had an acceptable level of chloroquine content and only 25% had acceptable dissolution properties. The study authors suggest that poor quality chloroquine may be among the causes of the high rate of resistance in these countries. Treating patients with poor quality medicines results in low bio-availability and drug under-dosage, so promoting the development of resistance – one of the major threats to public health.

In some countries, illegal manufacturing, distribution (including sales in market places and on streets) and

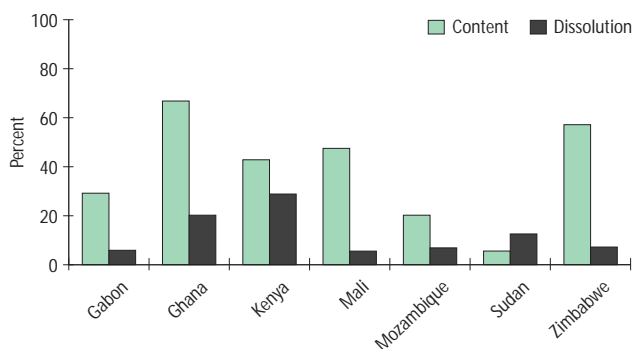
smuggling of medicines are widespread. Even manufacturers who fail to comply with good manufacturing practice (GMP) requirements can still produce medicines for domestic use and for export. Often controls on exported medicines are less stringent than for those used domestically.

Figure 2 Reports of counterfeit medicines by therapeutic class received by WHO 1999–2002



Source: WHO Database on Counterfeit Medicines

Figure 1 Percentage failures in ingredient content and dissolution in quality control tests on chloroquine tablets in seven sub-Saharan African countries



Source: The quality of antimalarials. A study in selected African countries. Geneva, World Health Organization; 2003.

Another major problem is that medicines are traded through several intermediaries and free-trade zones, and are sometimes repackaged and relabelled to hide their true source or identity, which can lead to the circulation of counterfeit medicines. Figure 2 gives the number of reports of counterfeit medicines, by therapeutic class, submitted to WHO from 1999 to 2002, and shows that the highest percentage concerned antibiotics.

Why must medicines be regulated?

The use of ineffective, poor quality, harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death. It also undermines confidence in health systems, health professionals, pharmaceutical manufacturers and distributors. Money spent on ineffective, poor quality medicines is wasted – whether by consumers



or governments. Governments need to establish strong national regulatory authorities (NRAs), to ensure that the manufacture, trade and use of medicines are regulated effectively, to protect and promote public health.

Box 1 Main reasons for regulating medicines

- There is an 'information asymmetry' between those who manufacture/sell medicines and patients/consumers, who are not equipped to make independent assessments of the quality, safety or efficacy of their medicines;
- Desperate patients may buy ineffective or even toxic medicines;
- Misuse of medicines, such as antibiotics, can have serious implications for individual and public health;
- Once medicines are prescribed to patients, others, such as dispensers and drug sellers, become involved. Regulation is needed to ensure that these interactions do not adversely affect treatment outcomes.

What is medicines regulation?

Medicines regulation incorporates several mutually reinforcing 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 Box 2.

Box 2 Principal medicines regulatory functions

- Licensing of the manufacture, import, export, distribution, promotion and advertising of medicines;
- Assessing the safety, efficacy and quality of medicines, and issuing marketing authorization;
- Inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines;
- Controlling and monitoring the quality of medicines on the market;
- Controlling promotion and advertising of medicines;
- Monitoring adverse reactions to medicines;
- Providing independent information on medicines to professionals and the public.

What makes medicines regulation effective?

Medicines regulation demands the application of sound medical, scientific and technical knowledge and skills, and operates within a legal framework. Regulatory functions involve interactions with various stakeholders (e.g. manufacturers, traders, consumers, health professionals, researchers and governments)

whose economic, social and political motives may differ, making implementation of regulation both politically and technically challenging.

To perform effectively, NRAs must be provided with the necessary political support and government inputs, including legal powers, and human and financial resources. However, these alone will not guarantee effective medicines regulation. NRAs also need strong public support and proper management. Good management requires appropriate strategies and methods to implement the various regulatory functions and enforce medicines regulation (Box 3).

Box 3 Factors contributing to effective regulation by NRAs

General

- Political will and commitment to regulation;
- Adequate supply of medicines at affordable prices (to avoid smuggling);
- Strong public support for drug regulation;
- Effective cooperation between the NRA and other government law enforcement agencies (e.g. customs and police);
- Sufficient qualified and experienced pharmaceutical and other professionals;
- Political environment favouring independent technical decision-making;
- Control of export and e-commerce of medicines.

Within the NRA

- Clear mission;
- Adequate medicines legislation and regulation;
- Appropriate organizational structure and facilities;
- Clearly defined roles and responsibilities;
- Adequate and sustainable financial resources, including resources to retain and develop staff;
- Appropriate tools, such as standards, guidelines and procedures;
- Strong cooperation and collaboration between NRAs and other stakeholders;
- Accountability and transparency;
- Good management system.

Key elements for ensuring effective regulation

Strong political will and commitment

In countries where political will and commitment are weak or absent, NRAs often lack adequate and sustainable human and financial resources, appropriate facilities and strong enforcement power. They are also vulnerable to external influence – for example, pharmaceutical manufacturers wielding strong political power may be able to influence decisions in their own

favour. To promote strong political commitment and support, NRAs must raise government awareness on the rationale for regulating medicines, the serious consequences of not doing so, and the threats posed by unsafe, ineffective, substandard and counterfeit medicines.

Strong public support

Experience in countries such as Australia, Canada, France, the UK and the USA, shows that the participation of consumers and public interest groups in medicines regulation enhances political support for the regulatory process, promotes NRAs' transparency and accountability, and protects them from negative external influence. It can also help to reduce conflicts of interest and corruption.

NRAs can increase public support through advocacy campaigns to encourage different sectors of the public to participate in groups through which they can voice their views on public health issues. Governments should encourage the creation of such consumer and other public interest groups, and establish mechanisms to enable them to participate in medicines regulation.

A clear mission and purpose

A clear mission statement, which includes the NRA's goals, is necessary to guide its work. Goals usually include the protection and promotion of public health by ensuring the safety, efficacy and quality of medicines, and their appropriate use; and ensuring the appropriateness of medicines information provided to the public and health professionals.

In some countries, NRAs are also assigned non-regulatory tasks, such as managing public sector drug supply or developing the pharmaceutical sector. Such additional duties will reduce the NRA's efficiency because it cannot focus solely on medicines regulation. The assignment of multiple missions with conflicting objectives can lead to conflicts of interest in fulfilling mandates, allocating resources or setting priorities. For example:

- Where NRAs are mandated to manufacture, import and/or distribute medicines, there is a risk of products being introduced to the market without undergoing the formal registration process. This leads to a double standard that can result in increased circulation of counterfeit and substandard medicines on national and international markets. Attempts to regulate often fail due to political interference.
- In medicines-exporting countries, where the main policy is to encourage exports and improve the national economy, the NRA's mission is often limited to the regulation of medicines for domestic use.

Governments should ensure that: NRAs are structurally independent of the government agency responsible for managing the national medicine supply system and should control it; regulatory controls are applied equally to the entire public and private sectors; and that the same regulatory standards are applied to medicines, whether for domestic use or export.

Comprehensive medicines legislation and regulation

In many countries medicines legislation and regulation are not regularly updated or are "imported" from other countries and do not reflect national realities. Countries should update their medicines legislation and regulations regularly to address new pharmaceutical issues as they arise. To protect the public from harmful and dubious medicines, legislation should cover all products for which medicinal claims are made, as well as related manufacture and trade activities, in the public and private sectors. Legislation should provide a basic legal framework and be flexible enough to provide adequate powers to the NRA (Box 4).

Box 4 Checklist for medicines legislation

- State the purpose of medicines regulation;
- Define the categories of medicinal products and activities to be regulated;
- Ensure legal provision for the creation of an NRA;
- Define the roles, responsibilities, rights and functions of all parties involved in the manufacture, trade and use of medicines;
- Set the qualifications and standards required for all those who handle medicines;
- Define the norms, standards and specifications to be applied in assessing the quality, safety and efficacy of medicinal products;
- State the terms and conditions for suspending, revoking or cancelling activity and product licences;
- Define prohibitions, offences, penalties and legal sanctions;
- Create mechanisms for ensuring transparency and accountability of regulation;
- Create mechanisms for government oversight to assess implementation of medicines regulation.

In addition, because medicines regulation deals with products, processes and practices that involve rapid scientific and technological change, the executive branch of the government responsible for drug regulation must be empowered to formulate new regulations, or to propose modifications to existing ones.

Appropriate organizational structure

Many countries organize their NRAs as small units or sections under divisions or departments of ministries



of health, which results in a low profile for the NRA. This organizational structure also tends to result in very limited government allocation of human, financial and other resources. In such circumstances, NRAs will have no independence in decision-making, acquiring and using resources, or in appointing and dismissing staff. Staff salaries will also be low, making it difficult to attract and retain qualified and competent staff. Overall, medicines regulation will be very weak.

Where NRAs have a high profile they are organized as a commission, board, statutory authority or department, with the legal power from government to acquire and use resources, and appoint and dismiss staff, and have independence in decision-making. In this way medicines regulation is well developed and operational.

Appropriate distribution of responsibilities

In some countries, regulatory functions come under the jurisdiction of a single agency with full authority over the command and control of all regulatory activities. In others, these functions are distributed between different authorities, either horizontally

(e.g. ministry of health, ministry of agriculture) or vertically (federal, state and local governments) and to function in an effective and coherent manner need coordination at national level. If horizontal or vertical distribution of responsibilities between different agencies is necessary, governments should:

- create a central coordinating body with overall responsibility and accountability for all aspects of medicines regulation for the entire country;
- ensure that the distribution of responsibilities between agencies is based on regulations or written terms of reference;
- develop coordination and information flow systems to support medicines regulation;
- build in a monitoring and evaluation system to assess implementation of regulation, identify shortcomings and their causes, and make timely corrections.

Adequate and sustainable human resources

For many countries the main problem is the shortage of qualified and skilled personnel. Low salaries, the scarcity of trained pharmaceutical and other essential professionals, a shortage of training institutions, inflexible recruitment procedures, lack of career structures and incentives, and the “brain drain” all contribute to the difficulties. Staffing problems cannot be solved quickly or easily (Box 5).

Adequate and sustainable financing

In developed countries and a few developing ones, such as Uganda and Zimbabwe, fees and charges levied for services represent a substantial proportion of NRA funding. For example, Australia’s Therapeutic Goods Administration recovers 100% of all regulation costs in this way. In Canada, the United Kingdom and the United States the NRAs recover 70%, 100% and around 50% of their costs respectively through fees. NRAs in developed countries charge higher fees than those in developing ones (Table 1), as the fees more accurately reflect the actual cost of services provided. Moreover the authorities have the power to control and use the funds to finance their activities. In developing countries fee revenues are usually transferred to the government treasury, making regulation exceptionally difficult to finance.

Experience to date indicates that government resources alone are insufficient to ensure that medicines regulation is sustainable and effective. Governments must revise their medicines legislation and introduce fee systems that reflect the real costs of services provided. However, special considerations, such as fee reduction or exemption, should be made for essential medicines, as is the case in most developing countries. NRAs should not be entirely dependent on fees and should receive some financial support from government sources.

Box 5 Checklist for addressing human resources problems

Governments should:

- Revise staff salaries to make them competitive;
- Ensure that staff are selected on merit and that recruitment and promotion procedures are flexible and attractive;
- Ensure that career structures and incentives are sufficiently appealing to prevent high staff turnover;
- Improve the knowledge and skills of NRA staff through in-house or external training programmes.

NRAs should:

- Involve experts from academia, research institutions, professional associations etc., to help with specific regulatory activities;
- Prioritize, streamline and computerize work processes;
- Train staff to carry out several regulatory functions (multi-skilling);
- Use team work and/or rotate staff to avoid frequent contact with regulated firms (which could lead to corruption);
- Use decisions made by reliable NRAs as the basis for decision-making in other NRAs;
- Participate in regional and subregional schemes, such as harmonization of regulatory processes and standards, and mutual recognition of regulatory decisions, to prevent duplication of effort, reduce workloads and save resources;
- Network and exchange information with other regulatory authorities.

Table 1 Medicines registration fees in US\$ – 1998/9

	New chemical entities	Domestically produced	Generics
Malaysia	100	100	100
Zimbabwe	1,000	38	1,000*
Cyprus	120	–	120
Uganda	300	200	300*
Cuba	700	700	700
Estonia	785	–	–
Tunisia	1,200	600	600
Venezuela	1,270	–	215
The Netherlands	15,000	–	5,000
Australia	120,000	–	2,500

* Imported products

Strong cooperation and collaboration between stakeholders

Enforcing drug legislation effectively requires NRAs and other government enforcement agencies, such as customs, police and prosecutors, to work together, but in many countries cooperation is non-existent.

NRAs should work with customs and police in inspecting products at ports, other points of entry and distribution outlets, detecting and investigating criminals involved in the illegal trade of medicines and counterfeiting, and apprehending and prosecuting criminals. NRAs should also seek the cooperation of health professionals, pharmaceutical and consumer associations, and other interested parties.

Transparency and accountability

Many NRAs do not make regulatory policies, administrative procedures, guidelines and criteria for decisions publicly available to all stakeholders. And many NRAs are not obliged to submit reports on their activities, either to the supervisory authorities or to the general public. Often decisions are not explained to clients in writing, and clients may not have access to an appeals system.

Lack of accountability and transparency mean that communication on medicines regulation between NRAs and their clients, government and the general public is likely to be lacking or highly unsatisfactory. Clients will not understand why certain regulatory decisions have been taken; governments will be ill-informed about the extent and significance of the activities of their NRAs; and the public will be unable to question any aspect of drug regulation because of lack of understanding of individual components and how they should be undertaken. But by building relationships with its stakeholders and promoting public confidence, NRAs can foster support for medicines regulation (Box 6).

Box 6 Checklist to ensure accountability and transparency

- Publish and disseminate regulatory policies, procedures and criteria for decisions made to all stakeholders;
- Discuss issues of common concern and procedures with stakeholders;
- Publish guidelines to promote understanding of medicines regulation and facilitate their implementation;
- Provide regular reports on activities to the supervisory authorities and the public;
- Create an independent appeals system for regulated firms;
- Establish mechanisms for dealing with complaints from the public.

Good management

In most developing countries, NRA management capacity remains very weak, with no written guidance for staff on the principles, practices and methods to be followed. Activities are seldom based on work plans, and tools, such as guidelines and standard operating procedures, are seldom developed and distributed to stakeholders. Monitoring and evaluation of implementation are rare, and are difficult because of the lack of information on regulatory activities and outcomes, and weak data management.

To function optimally NRAs must develop workplans with clear objectives, activities, time-frames and expected outputs. They must also introduce self-assessment programmes into their management systems to enable weaknesses in programme implementation to be identified and corrected quickly.

National regulatory authorities in an international context

In the absence of effective medicines regulation, increased globalization of the pharmaceutical trade can lead to the proliferation of harmful, ineffective, substandard and counterfeit medicines on national and international markets. With the rapid introduction of high-technology medicines into import, export and distribution networks (including e-commerce), the safety, quality and efficacy of medicines are matters of increasing concern. As an absolute minimum NRAs should:

- Ensure that all medicines manufacturing, importation, exportation, wholesale and distribution establishments are licensed. Activities and premises must comply with GMP and good distribution practice requirements.
- Before medicines are marketed, assess their safety, efficacy and quality.
- Monitor the quality and safety of medicines on the market to prevent harmful, substandard and counterfeit medicines from reaching the public.
- Regularly inspect and control the informal market, including e-commerce, to prevent illegal trade of medicines.



- Monitor advertising and promotion of medicines, and provide independent information on their rational use to the public and professionals.
- Participate in sub-regional and regional regulatory networks and international meetings of drug authorities to discuss issues of mutual interest and concern, facilitate timely exchange of information and promote collaboration.
- Monitor and evaluate performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective action.

NRAs must be responsive to the needs of the general public, and effective and efficient in discharging their duties. Any deficiency or delay in decision-making may enable harmful medicines to reach the market or lead to shortages of vital medicines, endangering lives.

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