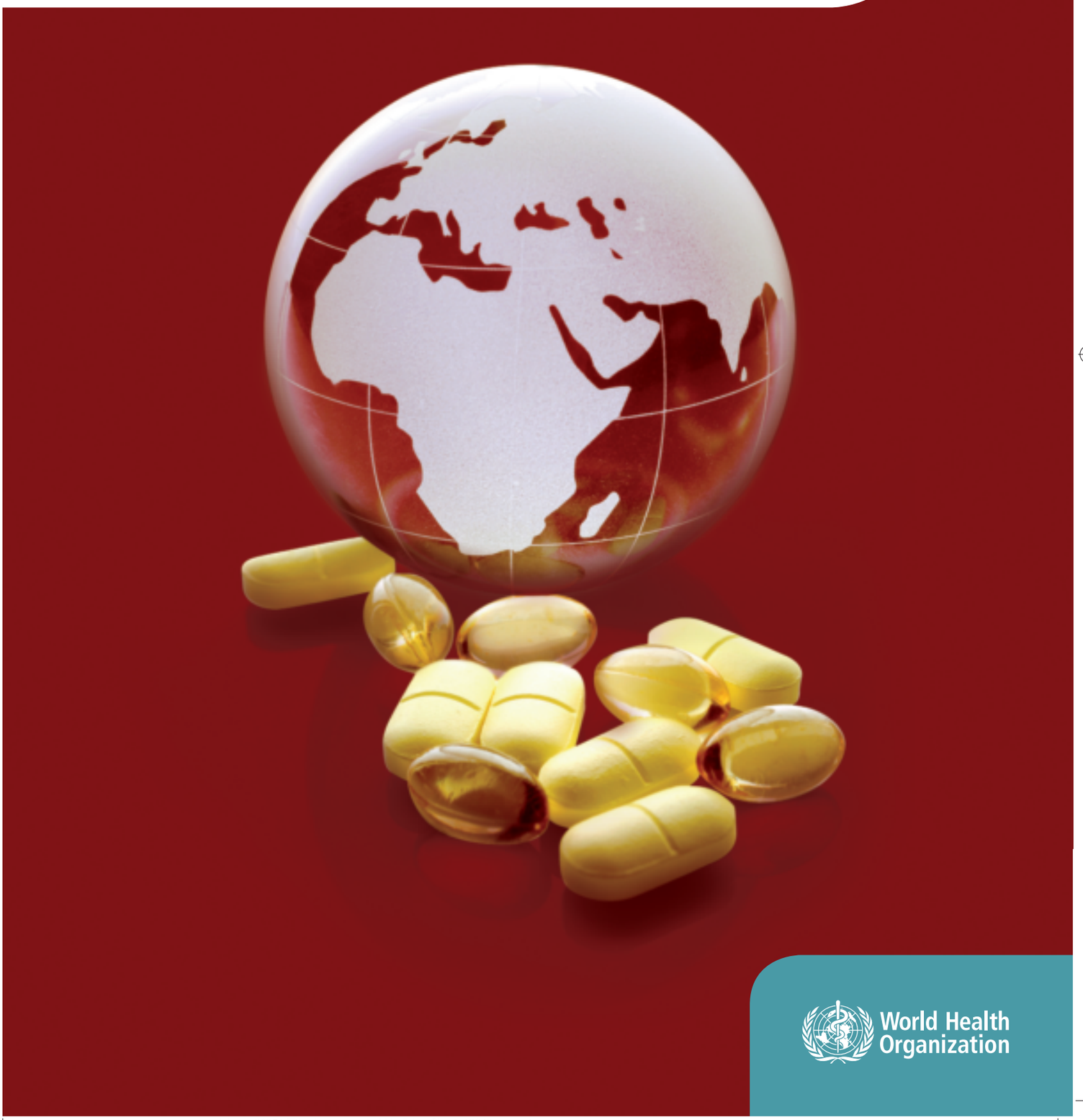
Assessment

of medicines regulatory systems in sub-Saharan African countries

An overview of findings from 26 assessment reports



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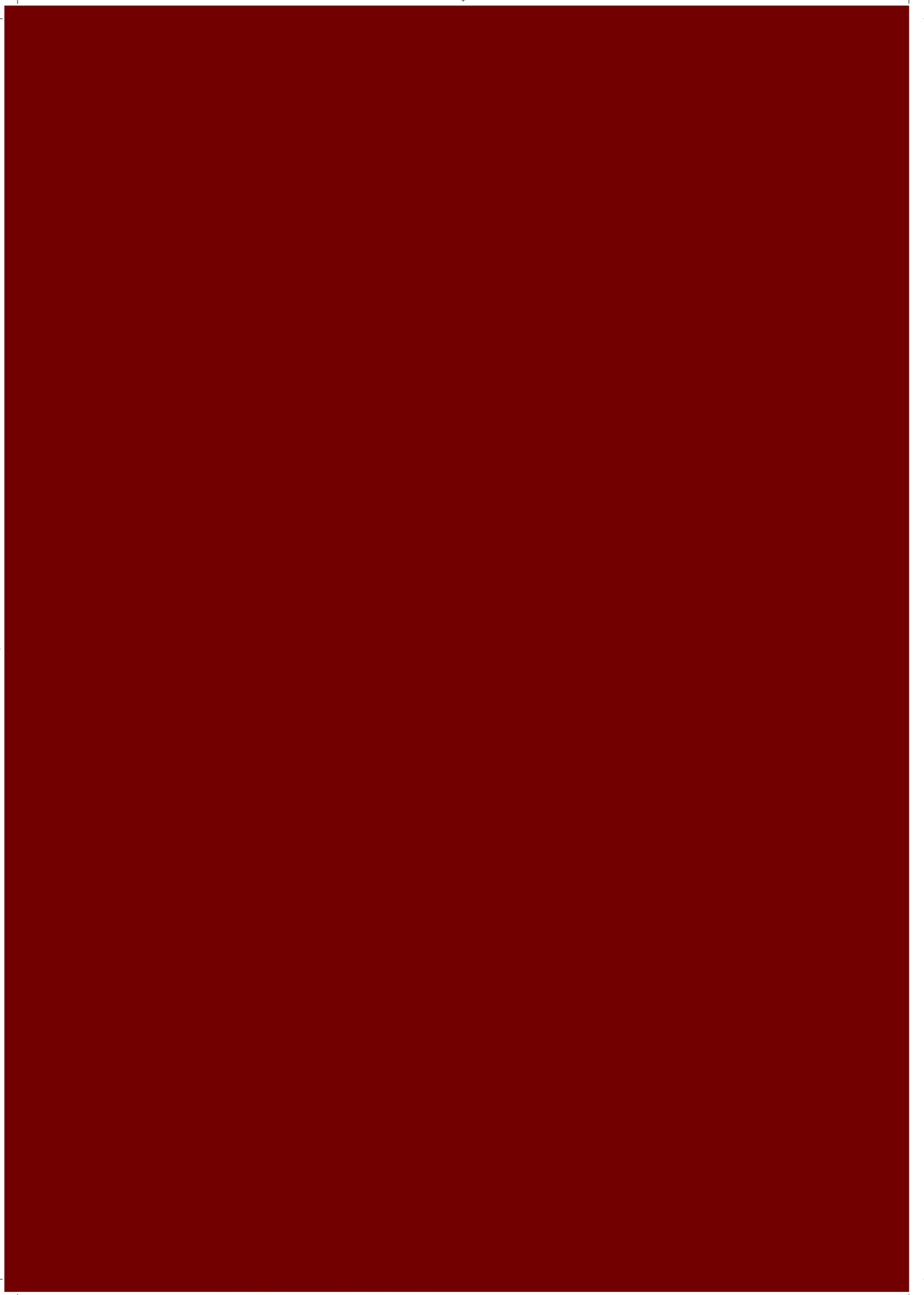

Contents

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The assessments were conducted by the following experts on behalf of WHO: Dr Adebowale Adeoye (WHO/DFID), Dr Abubakr Abdelraouf Alfadl (Sudan), Mr Mohamed Imadin Atabani (Sudan), Mr Benjamin Botwe (Ghana), Mrs Kari Bremer (Norway), Dr Andrew K. Chemwolo (Kenya), Mr Felix Peter Chizu (Zambia), Dr Mory Fofana (Guinea), Mrs Mariama Gamatie, Mr Ishmael Joseph, Mr Rutendo Kuwana (Zimbabwe), Mrs. A. C. Madukwe (Nigeria), Mr Einar Magnusson (Iceland), Ms. Gugu N Mahlangu (Zimbabwe), Dr Minkaila Maiga (Mali), Mr Deus Mubangizi (Uganda), Dr Anastasie Mulumba (WHO), Mr Viateur Mutanguha (Rwanda), Dr Margareth Ndomondo-Sigonda (Tanzania), Professor Tamás Paál (Hungary), Dr Alain Prat (WHO), Dr Nicole Ridolphi (France), Mr. Adetona Saka (WHO/DFID), Dr Burhani Othman Simai (Zanzibar), Mr Hiiti Sillo (Tanzania), Dr Stanley Soyona (EAC), Dr Ogori Taylor (Nigeria), Professor Amor Toumi (WHO), Dr Jean-Marie Trapsida (WHO-AFRO), Professor Charles Wambebe (WHO/DFID) and Mr Eshetu Wondemagegnehu (WHO).

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Dr Alain Prat further improved the WHO data collection tool for the assessments as well as a detailed guidance document for its use, building on the pioneering work of Eshetu Wondemagegnehu and Dr Valerio Reggi (WHO). He also prepared a background document synthesizing the main findings of 21 country assessments and giving conclusions based on his experience as a member of nine of the missions and from his ongoing work in assisting the regulatory authorities of the countries assessed.

Mrs Monika Zweygarth prepared the draft report. Dr Alain Prat, Dr Samvel Azatyan, Dr Amor Toumi and Dr Lembit Rägo provided valuable input.

Abbreviations

API	Active pharmaceutical ingredient
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
CIOMS	Council of International Organization of Medical Sciences
COA	Certificate of analysis
CPP	Certificate of pharmaceutical product
CTD	Common technical document
DMF	Drug Master File
EAC	East African Community
EMEA	European Medicines Agency
FPP	Finished pharmaceutical product
GCP	Good Clinical Practices
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
GLP	Good Laboratory Practices
GSP	Good Storage Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals forHuman Use
ISO	International Organization for Standardization
MA	Marketing authorization
MoH	Ministry of Health
NMRA	National medicines regulatory authority
NGO	Non-governmental organization
OECD	Organization for Economic Co-operation and Development
OTC	Over-the-counter
PQP	Prequalification Programme (WHO)
PV	Pharmacovigilance
QA	Quality assurance
QC	Quality control
SOP	Standard operating procedure
SPC	Summary of product characteristics
UMC	Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring hosting Global Database of Adverse Drug Reaction reports)
US FDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization

Executive summary

Medicines regulation is needed to ensure that all pharmaceutical products on the market are safe, effective and consistently meet approved quality standards [1].

WHO works with Member States in assessing national regulatory systems to identify gaps, develop strategies for improvement and support countries in their commitment to build national regulatory capacity.

This report synthesizes the findings of rapid assessments performed at national medicines regulatory authorities (NMRAs) in 26 African countries over the last eight years. It is mainly based on the reports provided to the countries by the assessment teams. Although the emphasis of the missions was on capacity-building rather than a standardized comparison of indicators, the findings are thought to give a reasonable overview of the regulatory situation in Africa at the time of the visits.

1. Country profiles

Most of the countries visited had limited economic resources as well as a high burden of illness, limited pharmaceutical manufacturing capacity and a diverse pharmaceutical supply chain.

2. Regulatory framework

Strengths: All countries had legal provisions in place which designated an NMRA and defined its main functions. Several countries were committed to giving their NMRAs more autonomy in terms of management and funding.

Weaknesses: The legal framework was complex, with unclear definitions of responsibilities, resulting in regulatory gaps and overlaps. Some NMRAs were not fully established. In many countries not all regulatory functions were operational.

3. Structure and management

Strengths: Overall, countries showed increasing awareness of the importance of independence, impartiality and transparency in medicines regulation. Many staff members were motivated and professional despite difficult working conditions.

Weaknesses: Most NMRAs lacked sustainable funding. There was a universal shortage of qualified staff and operational resources. Quality Management Systems covering regulatory procedures, specific development programmes to keep staff abreast of current technology and science, and specific measures to assure confidentiality and to avoid conflicts of interest were generally absent.

4. Medicines registration (marketing authorization)

Strengths: The majority of countries had a legal basis for medicines registration in place, and had drafted supporting documents for applicants and for assessors. Advisory committees were widely used, and to a certain extent expertise of external assessors was sought for medicines registration.

Weaknesses: Guidelines and assessment procedures were not up to WHO standards, and were often of an administrative rather than technical nature. There were wide-ranging exemption clauses not justified by a risk assessment, for example for public sector imports or donations. There were few mechanisms in place to ensure the impartiality and technical competence of external assessors. Scarce resources severely limited technical assessment of dossiers. In spite of resource constraints few countries relied on decisions made by other regulators such as stringent NMRAs or by the WHO Prequalification Programme. Regulatory decisions by other competent authorities were not widely recognized.

5. Licensing of activities

Strengths: Countries generally had legal provisions for licensing pharmaceutical activities, including manufacturing, wholesale, import/export, distribution and retail sale.

Weaknesses: Licensing was not implemented efficiently. This function was not under the sole control of the NMRA in most cases, and some of the authorities involved had no technical capacities. Poor coordination and poor information management resulted in regulatory gaps.

6. Import and export control

Strengths: In most countries, only medicines with marketing authorization were eligible for import.

Weaknesses: Systems to verify the marketing authorization or exemption status of products on importation were inefficient or absent in many countries. There was poor coordination among the authorities involved. Mechanisms to control exported medicines were either absent, or not stringently enforced.

7. Inspections

Strengths: Structures existed to inspect pharmaceutical establishments for compliance with national guidelines.

Weaknesses: This function was often shared with other authorities, and inspections were not well coordinated. Guidelines were not in line with WHO standards for Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP). Lack of qualified inspectors, transport and communication severely limited the number and quality of inspections conducted.

8. Quality control (QC)

Strengths: The majority of countries had a regulatory QC laboratory. Most laboratories had qualified staff, and many had adequate, serviceable equipment. Several laboratories were committed to implementing a QMS.

Weaknesses: Few laboratories had an effective QMS in place. QC testing was not used optimally to complement other regulatory functions.

9. Market surveillance (product quality monitoring, pharmacovigilance, control of promotion and advertising)

Strengths: Most countries had some legal provisions and structures in place to monitor the safety, efficacy and quality of medicines on the market.

Weaknesses: Implementation of post-marketing surveillance was poor. Quality monitoring was not prioritized based on risk, but was generally performed in case of complaints if at all. Few countries monitored adverse events to medicinal treatment or controlled promotion of pharmaceuticals systematically. Generally speaking, market surveillance measures were not sufficiently integrated with other regulatory activities.

10. Oversight of clinical trials

Strengths: The majority of countries had provisions in place to control ethical aspects of clinical trials.

Weaknesses: Few NMRAs authorized the performance of clinical trials in their countries, and therefore very few authorities monitored clinical trials after approval. Links with ethics committees were often weak or non-existent. GMP was not assured for investigational products.

Conclusion

Structures for medicines regulation existed in the countries assessed, and the main regulatory functions were addressed, although in practice the measures were often inadequate and did not form a coherent regulatory system. Common weaknesses included a fragmented legal basis in need of consolidation, weak management structures and processes, and a severe lack of staff and resources. On the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating on their markets or passing through their territories. Regulatory capacity should be built urgently in African countries, using the following approaches:

- Encourage and assist countries to assess their own regulatory systems in a systematic way in order to identify and address gaps.
- Work towards consistent implementation of all essential regulatory functions in African countries, based on the key provisions in the existing legal frameworks.
- Strengthen management structures, specific technical regulatory expertise and physical resources (both human and financial) available to NMRAs in Africa.
- Consider mechanisms for sharing the outcomes of regulatory assessments.

1. Introduction

1.1 Medicines regulation in developing countries

Medicines are essential to health care and must be available to the inhabitants of every country. Medicines regulation aims to ensure that medicines on national markets and in international commerce are safe, effective and of good quality, are accompanied by complete and correct product information, and are manufactured, stored, distributed and used in accordance with good practices.

Affordable products are increasingly becoming available which have the potential to reduce morbidity and mortality in resource-constrained countries dramatically. African countries import most of their pharmaceuticals. However, recently the African Union has started to promote local manufacture of medicines in Africa.

The increasing globalization of commerce and the merging of pharmaceutical companies are breaking down national boundaries in medicines supply. Substandard and counterfeit pharmaceutical products have been reported from all over the world [2]. The problem is greatest in developing countries, which have insufficient funds for medicines procurement, and even fewer resources to enforce quality standards and to protect the medicines supply chain.

The norms and standards for medicines quality are becoming more and more sophisticated. The assessment of new chemical entities is especially challenging. International norms and standards for medicines are thus more important than ever before. WHO continues to develop such norms and standards to serve as guidance for national regulatory systems. In practice however, quality standards of medicines are often adapted to the requirements in force in the destination country [3].

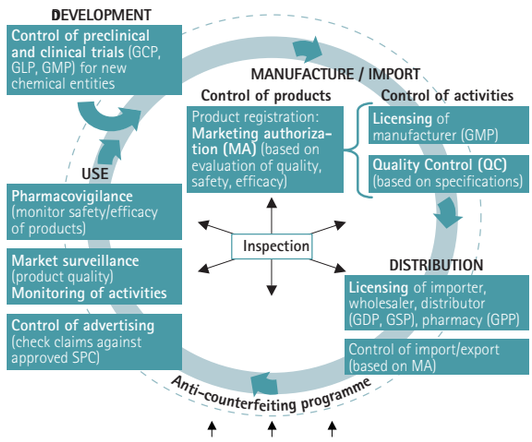
Regulating the increasingly complex channels of medicines supply requires constant vigilance, adaptation and considerable organizational capacity and resources. WHO's constitutional mandate requires it to support member states in implementing regulatory mechanisms to international norms and standards. This report presents the results of assessments of regulatory systems conducted in 26 sub-Saharan African countries (24 belonging to the WHO AFRO region) over the last eight years to identify regulatory gaps and to suggest priority activities to strengthen regulatory capacity.

1.2 Overview of regulatory elements

A host of challenges threatens the safety, efficacy and quality of medicines at every stage of their life cycle: Weaknesses in research and development, deficiencies in dosage form design, varying standards in ongoing production, damage during transport and storage, and inadequate use of products by prescribers and patients. An effective system must therefore provide the full range of regulatory functions, covering every stage of the cycle.

The main functions of an NMRA include control of pharmaceutical products by registration and post-marketing surveillance (quality monitoring and pharmacovigilance), as well as control of activities by licensing and inspection of manufacturers, importers, exporters, wholesalers, distributors, pharmacies and retail outlets, control of clinical trials and control of promotion of pharmaceuticals. These functions must work together to form a coherent medicines regulatory system (see Figure 1).

FIGURE 1: ALL FUNCTIONS OF A MEDICINES REGULATORY SYSTEM



African pharmaceutical markets are mostly generic markets. The main difference between the life cycles of originator and generic medicines is in the development phase. While for innovator medicines the focus is on safety and efficacy data (proven in preclinical and clinical trials), generic medicines are assumed to be safe and efficacious if they are proven to be interchangeable with originators, and the focus is essentially on quality.

1.3 Aim of this report

This report aims to give an overview of the legal basis, structures, processes and implementation of medicines regulation in African countries. It is anticipated that it will help policy makers, funders and other interested stakeholders to better understand the situation and to design appropriate actions to strengthen regulatory systems in Africa.

Objectives

The objectives of this report are:

- to highlight the main strengths and weaknesses of medicines regulation in African countries;
- to put the findings into the context of the global regulatory situation and of internationally recommended standards for effective medicines regulation; and
- to provide a baseline and perspective for future assessment strategies.

2. Method

The assessments summarized in this report were conducted during visits to NMRAs conducted in the period from 2002 to 2009 at countries' official request to WHO. These requests were motivated by sub-regional initiatives, collaborative projects for a situation analysis, and/or countries' willingness to strengthen national regulatory systems. Assessments included in this report were performed in 26 African countries. Four countries were visited twice; in these cases the most recent findings were taken into account.

The assessments were conducted by teams composed of WHO experts, staff from NMRAs and/or external consultants, acknowledged at the beginning of this report.

Written terms of reference and an agenda for the visits were agreed beforehand with the regulatory authority being assessed. The duration of the visits varied depending on the complexity of the country's regulatory functions, most visits took approximately three to five working days.

Data were collected by interviewing personnel, reviewing documents (manuals, records, reports, files), analysing data and/or observing activities. Findings were recorded on a comprehensive data collection tool developed by WHO [4], which was later complemented by a detailed guidance document [5]. A draft report was submitted to the regulatory authority after the visit together with a draft plan of action, and comments were invited.

This summary report was produced mainly on the basis of the reports provided to the NMRAs assessed. The completed data collection tools were consulted to verify and complete the findings where necessary.

In order to respect countries' confidentiality rights, countries are identified only by randomly assigned numbers in Sections 3.2 - 3.10 and in Annexes 2 -10. Countries are grouped into four geographic sub-regions of Africa (East, West, Middle, South[1]); Sudan as the only country of the North region has been included in the East region. Sub-units of NMRAs are uniformly referred to as departments, sub-units of countries are referred to as regions.

Limitations

The assessments included in this report took place over a period of eight years. The already comprehensive data collection tool developed by WHO was completed and updated during this time, introducing some variation in the indicators investigated.

The main aim of the visits, and the design of the tool itself, were geared towards identifying priorities for strengthening regulatory capacity. They were not primarily intended to provide comparable indicators of regulatory capacity over time. Not all questions were therefore answered in equal detail for all the countries.

The strengths and weaknesses identified by the authors of the country reports, on which this report is mainly based, reflect their technical judgement and the views expressed by the regulatory officials interviewed.

The evaluation visits were relatively short. Nonetheless, it is thought that the assessors identified the most important issues affecting medicines regulation in each country.

This report presents the situation at the time of the visits. With a few exceptions clearly marked as such, subsequent changes are not reflected.

1 Source of classification into subregions: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2009), World Population Prospects: The 2008 Revision, http://esa.un.org/unpp.

3. Results

3.1 Country profiles

The 26 countries included in this report constituted 88% of the population of sub-Saharan Africa in 2007. Some key economic and health-related data are summarized below, together with corresponding data for OECD countries around the world. Details are shown in Annex 1.

ECONOMIC INDICATORS

Indicator	26 African countries	OECD countries[2]
Per capita Gross Domestic Product at average exchange rate (US-$, 2006) *	115 (Burundi) – 7 800 (Gabon) **Median: 611**	7 333 (Turkey) – 89 123 (Luxembourg) **Median: 36 714**
Per capita total expenditure on health at average exchange rate (US-$, 2006)	7 (Ethiopia) – 425 (South Africa) **Median: 32**	352 (Turkey) - 6 719 (USA) **Median: 3 317**
External resources for health as % of total health expenditure (2006)	1 (South Africa) - 60.3 (Mozambique) **Median: 22**	**0**
Out-of-pocket expenditure for health, as % of total health expenditure (2006)**	6 (Botswana) - 75 (Cameroon) **Median: 39**	6 (Netherlands) – 52 (Mexico) **Median: 17**

* Calculated as: Per capita total expenditure on health at average exchange rate (US$) / Total expenditure on health as proportion of gross domestic product. Not shown in Annex 1.

** Calculated as: Private expenditure on health as proportion of total expenditure on health × Out-of-Pocket expenditure as proportion of private expenditure on health.

Source: WHO World Health Statistics 2009 [6]

In African countries:

- Limited resources were reflected in very low per capita expenditures on health (median: 32 US-$ per inhabitant per year);
- Donor dependence was high (median: 22% of health expenditure); and
- Out-of-pocket expenditure by patients was high (up to 75% of health expenditure; median: 39%). A large part of out-of-pocket expenditure for health is generally used for medicines [7].

2 Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States.

HEALTH INDICATORS

Indicator	26 African countries	OECD countries
Life expectancy (years)	46 (Chad, Zambia) – 59 (Gabon, Senegal) **Median: 52**	73 (Hungary, Turkey) – 83 (Japan) **Median: 80**
Neonatal mortality rate (per 1000 live births, 2004)*	17 (South Africa) – 64 (C. Ivoire) **Median: 41**	1 (Iceland, Japan) – 16 (Turkey) **Median: 3**
Prevalence of tuberculosis (per 100 000 population, 2007)*	135 (Benin) – 1 104 (Djibouti) **Median: 447**	3 (Iceland, USA) – 126 (Korea) **Median: 9**
Prevalence of HIV among adults aged ≥ 15 years (per 100 000 population)*	757 (Niger) – 22 757 (Botswana) **Median: 2 878**	9 (Japan) – 452 (USA) **Median: 125**
Percent of years of life lost due to communicable diseases (2004)*	57 (Sudan) – 87 (Malawi) **Median: 81**	3 (Hungary) – 26 (Turkey) **Median: 5**

* Not shown in Annex 1

Source: WHO World Health Statistics 2009 [6]

- African countries had a high burden of illness and death due to infectious and communicable diseases. Safe, efficacious, good quality medicines exist to treat these diseases, but health benefits will be achieved only if good quality products are made available and used appropriately.

PHARMACEUTICAL SECTOR

Indicator	26 African countries (data from country reports)
Manufacturers	> 20 in five countries: Ghana, Kenya, Nigeria, South Africa
Distributors	9 (Djibouti) – 296 (Sudan), private and public sector
Retail pharmacies	9, also acting as distributors (Djibouti) - 1600 registered pharmacies and many other outlets (Nigeria), 1186 pharmacies and 9814 other licensed outlets (Ghana)

The pharmaceutical sector data included in country reports indicated that African countries generally had:

- Limited pharmaceutical production capacity, most depended mainly on imports.
- Some pharmaceutical manufacturing activity catering mainly for the domestic and regional demand; however there were some exporting countries; and
- A diverse distribution chain, with some types of unauthorized outlets suggesting the presence of an informal market (see Annex 1).

The situation in African countries

Most of the African countries included in this report have very limited health budgets, and limited resources for medicines regulation. There are indications of the presence of parallel, unregulated medicines markets, posing serious risks for individual and public health.

Nevertheless, differences exist in the efficiency of the regulatory measures implemented by countries, illustrating the impact of political commitment and resources allocated to medicines regulation.

In all countries, the challenge remains to maintain comprehensive, effective regulatory systems in a context of rapidly evolving pharmaceutical technologies and an increasingly globalized market.

3.2 Regulatory framework

Legislation

Written laws, Acts or Statutes enacted by Parliament give the NMRA the power to control medicines. Regulations prepared under the authority of an Act (the "Enabling Act") provide details of how regulatory functions are to be carried out. Based on the legislation, guidelines are needed to interpret the legislation and to advise on how to comply with a regulation.

The legal framework should allow effective implementation and provide adequate powers to the NMRA. 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. Countries should update their medicines legislation and regulations regularly to reflect national realities and to address new pharmaceutical issues as they arise [1].

KEY FINDINGS (SEE ANNEX 2 FOR DETAILS)

+ In most countries, legislation had evolved over many years. The enabling act for medicines regulation was enacted later than 2000 in only three countries.
– In many countries, the way in which the legal and explanatory texts were drafted affected the efficiency of medicines regulation. Successive regulations and decrees created a complex legal framework with overlaps and grey areas.
– Regulations for specific regulatory functions were missing in some countries, especially where a transformation process of the NMRA was taking place.

Regulatory scope

In the last few decades, expansion of the regulatory scope has been considered in many countries [8]. A medicine has been defined as "Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient" [9]. In addition to conventional medicines for human use, this definition also includes biological medicines (including vaccines and blood products), veterinary medicines, and traditional and herbal medicines, although the latter category is challenging to define and to regulate [10].

All types of medicines should be regulated by the NMRA. At the same time, implementation of medicines regulation should not be compromised by other, non-regulatory activities performed by the NMRA. [8]

KEY FINDINGS (SEE ANNEX 2 FOR DETAILS)

+ Seventeen of 26 NMRAs (65%) had the mandate to control veterinary medicines. In four countries veterinary medicines were controlled by another Ministry, such as the Ministry of Agriculture or Livestock.
+ Eighteen of 26 NMRAs (69%) had some policy or provisions to deal with traditional or herbal medicines, eleven of these registered traditional or herbal medicines, another two[3] were about to start doing so.
– NMRAs in eleven countries[4] (42%) regulated a wide scope of products, which included foods, poisons, pesticides, bottled water, cosmetics and/or animal food supplements.
– In seven countries[5], the NMRA was involved in designing and implementing national medicines strategies, implementing legislation or coordinating public sector medicines supply; in one case a clearly distinguished unit was in charge of policy issues.

Organizational forms

The choice of a specific organizational form will have an impact on the autonomy, visibility and accountability of an NMRA. These factors can in turn affect the organization's efficiency in medicines control.

3 Country 02, Country 16 (no regulations yet)
4 Countries 02, 03, 04, 11, 12, 14, 16, 19, 23, 24, 26
5 Countries 01, 09, 13, 17, 18, 22, 23; in Country 15 policy activities and regulatory functions were carried out by different organizational units of the NMRA

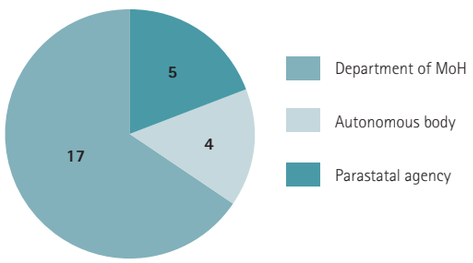
One central authority should be accountable for the overall effectiveness of medicines regulation. It should have the legal power from government to acquire and use resources, recruit and dismiss staff, and make independent decisions.

KEY FINDINGS (SEE FIGURE 2 AND ANNEX 2 FOR DETAILS)

Historically, most NMRAs in Africa started out as departments under the Ministry of Health. Organizations of this type have little autonomy. They cannot recruit their own staff, nor can they offer adequate salaries to attract and retain qualified experts. With the maturation of regulatory systems, some countries are moving away from this model, and are establishing their NMRAs as autonomous bodies or as centralized parastatal agencies with their own management structures.

- Seventeen of 26 authorities (65%) were departments of the Ministry of Health, with very little or no autonomy to manage their own funds and human resources.
- Seven NMRAs (27%, including four departments of MoH and two autonomous bodies) were in transition or not formally constituted at the time of the visit.

FIGURE 2: LEGAL FORMS OF NMRAS AT TIME OF VISIT



Regulatory functions

The responsibilities assumed by the authority should cover all medicines regulatory functions and should be performed in a balanced fashion.

If functions are distributed between different authorities, either horizontally (e.g. ministry of health, ministry of agriculture) or vertically (federal, state/regional and local governments), a central coordinating body should be accountable for all aspects of medicines regulation in the country [1].

KEY FINDINGS (SEE FIGURES 3A AND 3B, AND ANNEX 2 FOR DETAILS)

+ Four of the 26 NMRAs (15%) had all five main functions shown in Figure 3B (marketing authorization, licensing, inspection, quality control and pharmacovigilance) under their umbrella.
+ Seventeen NMRAs (65%) had access to a functional national regulatory QC laboratory, seven of these laboratories were part of the NMRA. In one of the remaining countries, there was an NMRA lab which had ceased to function several years earlier.

– Most countries had fragmented regulatory systems. Gaps and overlaps of responsibilities were common, especially in licensing (involving the Ministry of Public Health or Ministry of Trade) and inspection (involving Pharmaceutical Councils, regional authorities or public health inspectorates).
– Decentralization and cooperation between authorities was problematic; 12 reports highlighted the lack of communication at operational level.
– In many cases, regulatory functions were not operational and in some cases not even delegated by law to the national medicines regulatory authority.

FIGURE 3A: PERFORMANCE OF REGULATORY FUNCTIONS

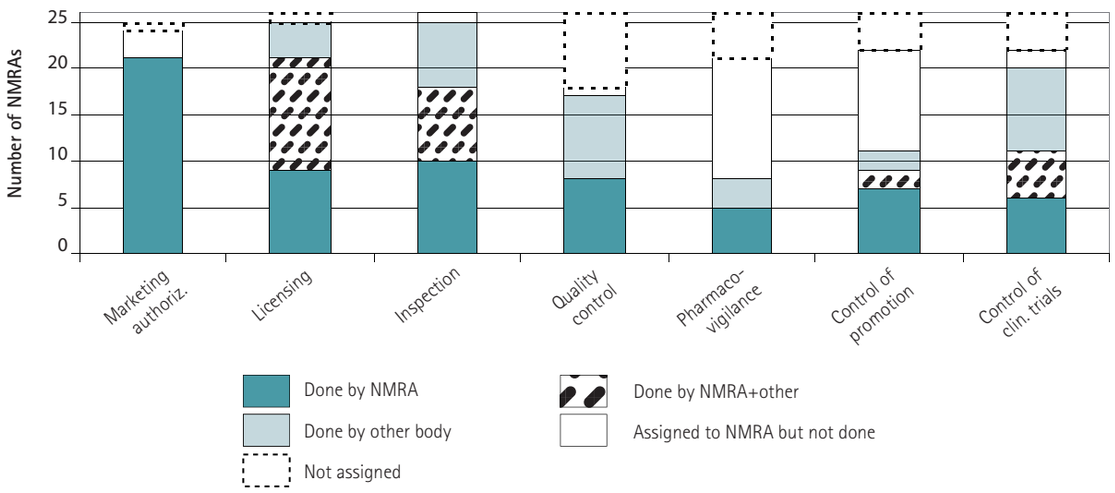


FIGURE 3B: COMBINATIONS OF FUNCTIONS WHOLLY OR PARTLY UNDER THE UMBRELLA OF NMRAS

Number of main functions performed by NMRA*	Marketing authorization	Licensing	Inspection	Quality control	Pharmaco-vigilance	Number of NMRAs
5 / 5	■	■	■	■	■	4
4 / 5	■	■	■		■	9
	■	■	■	■		3
	■		■	■	■	1
3 / 5	■	■	■			1
	■	■			■	3
	■		■	■		1
2 / 5	■	■				1
	■				■	1
1 / 5	■					1
0 / 5	(NMRA not yet established)					1
Total						26

* Including functions performed jointly with one or more other authorities

3.3 Structure and management

Funding

Sustainable funding for NMRAs should be derived from various sources:

1. Fees, which should contribute significantly to operational costs but should not discourage applications,
2. Public funding, to make NMRAs less dependent of the parties which they are mandated to regulate, and
3. Donations to supplement limited public funds.

NMRAs should have the autonomy to retain the fees collected for services provided, and to use them for their own purpose.

KEY FINDINGS (SEE ANNEX 3 FOR DETAILS)

+ Most NMRAs derived their funding from more than one source, although the proportions varied from one country to another.
+ Fees were commonly charged for initial marketing authorization, renewal and retention. More rarely, fees were charged for importation of medicines, inspection, analysis of samples and registering persons and premises.
– Generally, the fees were lower than the cost of services rendered, and were not retained or redistributed in full.
– At the time of the visits, nine NMRAs depended on government funding, with all fees paid directly to the treasury and not redistributed. Four of these also received donor funding. Funds allocated to the NMRAs by the respective States were not always released on time.
– **None of the NMRAs assessed had adequate and sustained funding for its operations**.

Human resource management

Personnel engaged in medicines regulation should be individuals of integrity and appropriately trained and qualified. Human resources development programmes should be made available to enable staff to keep up with developments in pharmaceutical science and technology [8].

KEY FINDINGS (SEE ANNEX 3 FOR DETAILS)

In general, human resource management was either non-existent or, where it existed, inefficient. This was the case especially where the NMRA was at a low level of hierarchy within the Ministry of Health. As a result, **lack of qualified staff affected critical regulatory functions (see Sections 3.4, Marketing authorization, and 3.7, Inspections).** Specific shortcomings included the following:

– Only two of the 26 NMRAs (8%) had a human resource development plan, which was however not specific to the tasks of the NMRA. Specific training needs and difficult access to sources of current information were noted in most countries.
– Job descriptions for key personnel were described as absent in five countries, and as unclear or outdated in four. Four reports mentioned the absence of an organigram.
– In some authorities, responsibilities were not assigned appropriately. One NMRA director was at the same time the director of the national laboratory, resulting in an unmanageable workload. Three others[6] were simultaneously in charge of public sector medicines supply or tenders, creating apotential conflict of interest.
– Five reports[7] mentioned the absence of a legal advisor on the NMRA's payroll.

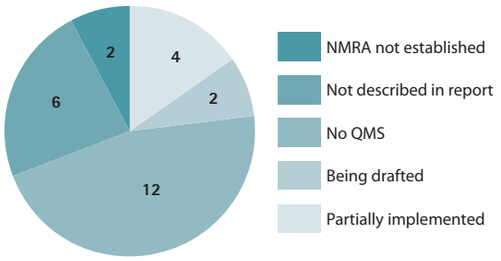
Quality management system

NMRAs perform critical and sensitive functions such handling and assessing marketing application dossiers containing confidential information, inspecting facilities and handling site master files.

A quality management system (QMS) should ensure that the operations of an NMRA are carried out to defined, uniform standards, and that each step of the regulatory processes is identified and documented.

6 Countries 13, 20 and 21
7 Countries 02, 12, 17, 18 and 23

FIGURE 4: PRESENCE OF QUALITY MANAGEMENT SYSTEMS (QMS) AT NMRAS



(see Annex 3 for details)

KEY FINDINGS (SEE FIGURE 4 AND ANNEX 3 FOR DETAILS)

+ Four NMRAs (15%) were in the process of implementing a QMS and had elements of the system in place, two others were drafting a system.

– None of the NMRAs had implemented a comprehensive QMS.

IMPARTIALITY AND TRANSPARENCY

Medicines regulation is a public policy that restricts private sector activities in order to attain social goals – the promotion of public health - set by the State. Conflicting interests therefore need to be recognized and managed appropriately.

To provide credible regulatory services, NMRAs must have specific measures in place to avoid conflict of interest in decision-making, to ensure confidentiality, to make their rules and decisions transparent, and to consult with stakeholders.

KEY FINDINGS (SEE ANNEX 3 FOR DETAILS)

+ Nine of the 26 NMRAs had set up websites at the time of the visits. Five of these were in need of updating, one had links which were not functioning correctly. As at November 2009, five additional sites were identified, one of the initial nine could no longer be found [11].

+ Consultation with stakeholders took place in most countries, although it tended to be limited to specific issues (e.g. regulations) or groups (e.g. professional associations).

– Current information was not always publicly available: lists of approved products or establishments were often missing and/or outdated. Little information was made public on decision-making.

– **Twenty-three[8] of 26 NMRAs (88%) had no written declarations of interest and confidentiality agreements in place,** although some had general rules of conduct such as a code for civil servants. In the three countries which did have a specific written system, this did not apply to all technical staff involved in regulatory functions.

3.4 Medicines registration (marketing authorization)

Authorization of medicines for sale in a country, based on a scientific assessment of their safety, efficacy and quality, could be considered as the core regulatory function.

To assess applications for marketing authorization, NMRAs need the following:

1. **Legal basis,** giving the NMRA the power to grant, renew, vary, suspend and withdraw of marketing authorization
2. **Guidelines for applicants,** setting out the conditions, content and format of applications, AND the detailed technical requirements against which dossiers will be assessed, based on international guidelines [e.g. 12, 13, 14]
3. **Standardized operating procedures** to assess the submissions, and standard formats to communicate and publish the outcomes
4. **Expert assessors** in adequate numbers and with specific, current expertise
5. **Logistics** for management, secure storage, retrieval and exchange of data with other regulatory departments, as well access to current scientific and technical information
6. **Mechanisms to consider other, stringent NMRAs' decisions**

KEY FINDINGS (SEE FIGURE 5 AND ANNEX 4 FOR DETAILS)

+ Some evaluation of technical documents was performed in 19 of 26 countries (73%) to varying degrees of stringency at least for generic medicines.

– Although the aim of the visits was to identify critical gaps (not to document the consistency of the technical

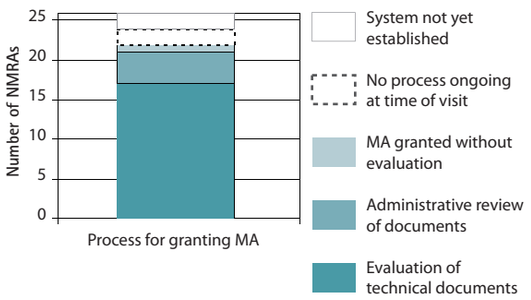
8 All except Countries 11, 15 and 26

evaluation process with WHO guidance), it can be concluded that the technical standard of evaluations was generally not in line with WHO standards. The reports from four countries[9] mentioned that guidelines did not require proof of bioequivalence for generics. At least three NMRAs[10] did not require the manufacturer to have GMP certification. At least six NMRAs[11] did not assess summaries of product characteristics (SPC).

– The capacity to assess applications for new innovator products was almost non-existent in most countries; one country relied exclusively on well-qualified external assessors, but organizational issues caused delays in assessments.

– NMRAs in seven countries conducted either only an administrative review of documents or no review at all at the time of the visit.

FIGURE 5: PROCESSES IN PLACE FOR GRANTING MARKETING AUTHORIZATION FOR MEDICINES



1. Legal basis and regulations

+ Eighteen of 26 NMRAs (69%) operated on a legal basis which empowered them to assess applications for marketing authorization, with regulations that briefly outlined the requirements or listed the components of dossiers to be submitted for different types of products.

+ Provisions for renewal of marketing authorizations were in place, usually after 5 years.

– Seven countries had provisions which exempted wide ranges of products (such as public sector imports or donations) from registration or from specific requirements irrespective of quality risk. For example, in one country, all oral solid-dose anti-infectives were exempt from in vivo bioequivalence studies, regardless of their biopharmaceutical classification.

2. Guidelines

The aim of the visits was not to verify compliance with WHO guidance systematically, but rather to assess the adequacy of national guidelines and to identify gaps. Some countries had guidelines which described the required content of submissions and gave brief instructions, but did not give sufficient guidance on technical issues such as bioequivalence and stability. Others described only the administrative steps, yet others provided only checklists. A specific format for submissions was not required in any of the countries.

– Only three NMRAs (12%) provided detailed technical guidelines, although this did not necessarily mean that they were in line with all applicable WHO guidance.

3. Procedures for assessment

Written standard operating procedures for dossier assessment were either absent altogether, or they described only administrative steps such as checking the completeness of dossiers, payment of fees or inclusion of samples, or they were checklists of the elements of the assessment methodology.

– Adequate SOPs for dossier assessment were in place in only three countries.

Timeframes for assessment of applications ranged from 3 months to 5 years, depending on the complexity of assessments and available resources. Fast-track mechanisms existed for certain needed product types.

– Although overall assessment time frames were long, little time was available for a thorough in-depth assessment by experts due to scheduling difficulties and backlogs.

4. Expert assessors

Most NMRAs had formal advisory committees. However, not all committees were operational, bringing assessment to a halt in two countries. Eleven countries used external experts, two of them exclusively. Appointment of committee members and experts was not necessarily based on specific regulatory expertise, and provisions for confidentiality and declaration of interest were lacking in most countries (see also Annex 3). Two

9 Countries 05, 09, 20 and 25

10 The reports state that GMP was verified in Countries 02, 11 and 05 (in the latter country the system was not yet functional); and that it was not required in Countries 04, 16 and 18.

11 Seven reports stated that SPC were not being assessed (countries 02, 03, 04, 13, 14, 22 and 24). Where SPC were assessed, they were not necessarily published as part of marketing authorization (see also Annex 4).

reports[12] mentioned the short preparation and meeting times available for committee members to make their decisions, meaning that they may not be able to read all documents and carry out any real assessment.

– Twenty-four of 26 country reports (92%) mentioned the shortage of adequately qualified assessors as an obstacle to timely dossier evaluation.

5. Logistics

– Only four NMRAs (15%) had appropriate archiving space to store confidential data securely.

– Only six of 26 countries (23%) had coherent, networked computerized systems designed for medicines registration in place. Nine (35%) had only manual systems.

The latter shortcoming affected transparency and information-sharing with other departments. Lists of registered products were not readily available, which made it difficult to verify the registration status of medicines circulating in the market and those being imported. The countries which did publish a list did not include the approved summaries of product characteristics (SPC), needed to verify package inserts, information for health professionals and advertising claims.

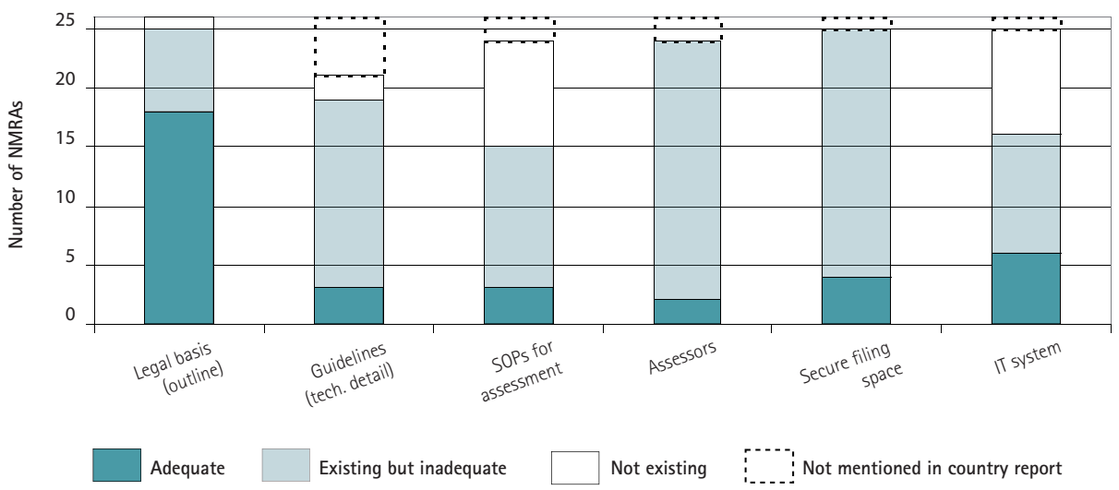
6. Recognition of other NMRA's decisions

Certificates of pharmaceutical products (CPPs) issued under the provisions of WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce [15] were commonly requested as part of applications, but usually without considering the capacity of the issuing regulatory authority to certify that the data on the certificates were correct. Conversely, one report from an exporting country[13] mentioned that the NMRA *"issues CPP without ascertaining that all prerequisites as specified by WHO are fulfilled"*.

– Only two NMRAs (8%) explicitly relied on other regulatory bodies/organizations which they considered stringent, including the WHO Prequalification Programme [16] in one case.

The lack of mechanisms and procedures that would enable NMRAs to benefit from the scientific assessments and inspections carried out by other well resourced and established regulators is a major cause of concern, as most of the authorities in the region have limited human resources and scientific expertise.

FIGURE 6: RESOURCES FOR MEDICINES REGISTRATION



12 Countries 03 and 26

13 Country 24

3.5 Licensing of activities

Licensing of pharmaceutical establishments

As can be seen from the country profiles, health budgets in African countries are low, high percentages of health costs are paid out of pocket, and there are many types of medicines outlets not managed by a pharmacist. Concerns about the parallel medicines market were voiced in most reports, such as this typical statement[14]: *"The illicit medicines market has become a real plague in [the country]. All therapeutic classes can be found, including psychotropic medicines, and there is no national strategy to combat this situation".*

A mandatory system of licensing manufacturers, wholesalers/distributors and retailers is essential to ensure that medicines conform to acceptable standards of quality, safety and efficacy until they reach the end user. Licensing must be complemented by inspections (see Section 3.7) and market surveillance (see Section 3.9) to monitor and enforce compliance.

NMRAs should ensure that all premises and practices used to manufacture, store, distribute and dispense pharmaceutical products comply with current guidelines on Good Manufacturing Practice [17], Good Storage Practice [18] Good Distribution Practice [19] and Good Pharmacy Practice (GPP) [20].

KEY FINDINGS (SEE ANNEX 5)

+ All countries except one had systems in place to license pharmaceutical establishments.

– GMP was not required in at least 9 countries[15]. In at least two countries where GMP was required[16], none of the established manufacturers had GMP certification.

– Only five of 26 countries (20% - see Annex 7) had published GMP guidelines meeting WHO standards (two had national texts, and another three used the WHO text). Only one country (4%) had adequate GDP guidelines.

– Authorities other than the NMRA were involved in licensing in 16 countries (62%), resulting in overlaps, grey areas and gaps in the control of pharmaceutical activities.

– Decentralization of licensing, involving regional authorities, was not organized efficiently. Lack of coordination between departments and with enforcement agencies was commonly highlighted.

– Licences or renewals were granted without inspection in some instances.

– In practice the requirements for Good Manufacturing Practice, Good Distribution Practice and Good Pharmacy Practice were poorly enforced. For example, In one country[17] only a single one of many established manufacturers was licensed.

3.6 Import and export control

A system to grant marketing authorization for pharmaceutical products is not in itself a sufficient mechanism to control the quality of products circulating in the country. It should be complemented by a range of other control measures (see also Figure 1), including the authorization of each import act of pharmaceutical products.

Each act of importation should be subject to authorization by the NMRA on the basis of the product's registration (marketing authorization) status.

Products for export should be subject to the same standards as those for domestic consumption.

KEY FINDINGS (SEE ANNEX 6 FOR DETAILS)

– Control of imported products was weak. In at least eight countries[18] (31%) there was no efficient system to verify the marketing authorization status and exemptions for imported products.

– Cooperation with police and customs was consistently described as problematic.

– Mechanisms to control exported medicines were either absent or not stringently enforced. One report[19] mentioned manufacturers' illegal practice of issuing "free sale certificates", which leaves all control to the receiving country.

14 Country 17
15 Countries 03, 06, 08, 09, 12, 14, 17, 24 and 25
16 Countries 02 and 05
17 Country 04
18 Countries 07, 09, 13, 18, 22, 23, 24 and 25
19 Country 02

3.7 Inspections

Inspection of pharmaceutical facilities should enable medicines regulatory authorities to monitor whether pharmaceutical activities are carried out in accordance with approved standards and guidelines. The efficiency of inspections has a direct impact on the extent to which medicines control is enforced.

A legal basis must be in place for inspections and enforcement of compliance with relevant good practices. Routine inspections should be planned and implemented to verify this compliance regularly.

A quality management system [21] should ensure that inspections are planned, conducted, documented and followed up in a consistent way, based on risk assessment.

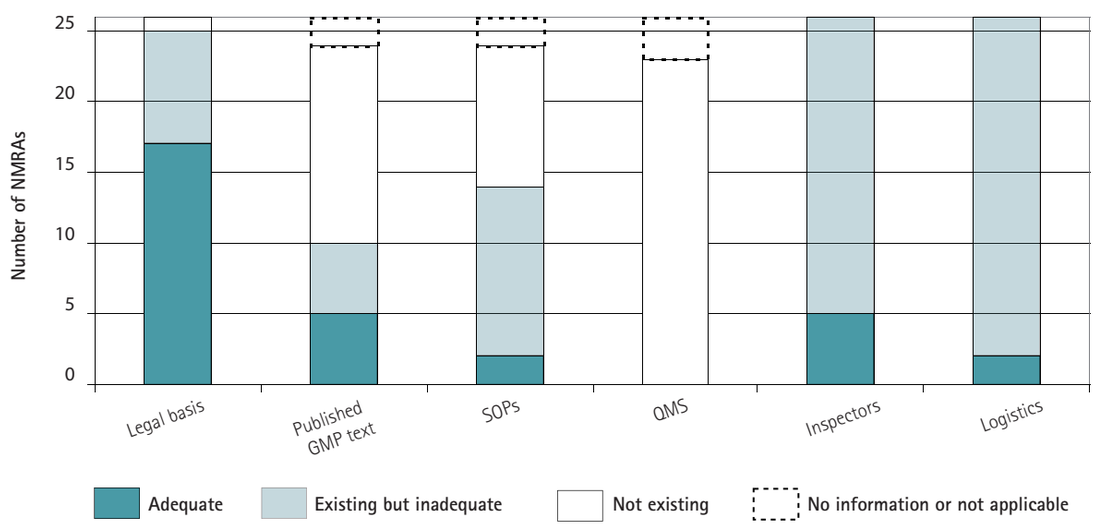
Enough qualified inspectors and sufficient logistic resources must be available to cover the geographic area to be regulated.

KEY FINDINGS (SEE FIGURE 7 AND ANNEX 7 FOR DETAILS)

+ A legal basis empowering the relevant authority to perform inspections was in place in 17 countries.
– SOPs for inspection, if any, were mostly in checklist format and were not comprehensive.
– No NMRA had a comprehensive quality management and planning system for inspections in place.
– Shortages of qualified inspectors were a universal problem. The need for specific training of inspectors in current GMP was commonly highlighted.
– Potential conflicts of interest were noted in at least three countries[20].
– Inadequate logistic resources, especially means of transport and communication, were a major constraint.

The effectiveness of inspections suffered from these constraints.

FIGURE 7: RESOURCES FOR INSPECTIONS



20 In Countries 02 and 05 the inspectors were also permitted to be supervisors/technical directors of pharmacies. In Country 03 pharmacists from distribution channels and manufacturers were used as inspectors

3.8 Quality control

Quality control (QC) aims to verify that products comply with the specifications of the marketing authorization. Even if pre-marketing samples meet defined standards, the same quality standards may not be met by each batch of product put on the market. QC testing of post-marketing samples thus acts as a deterrent against negligent or fraudulent manufacturing and trading practices [8].

NMRAs should have access to a quality control laboratory with adequate capacity to undertake quality surveillance.

QC facilities must have enough qualified personnel and the necessary equipment and materials, and must operate according to established standards [8]. A Quality Management System (QMS), such as ISO 17025 [22], provides a framework for QC laboratories to operate according to defined procedures and standards. WHO's guidance on Good Laboratory Practice [23, 24] provides detailed advice on organizational and technical issues.

If dossiers are assessed and samples tested, good collaboration between assessors and laboratory staff needs to be in place.

KEY FINDINGS (SEE ANNEX 8 FOR DETAILS)

+ A QMS was in place at five (29%) of the 17 functioning regulatory laboratories; three others had partial systems which were lacking essential elements and were not fully operational.
+ Satisfactory staffing and equipment were in place in the majority of cases, but six laboratories were housed in inadequate buildings.

Ten reports mentioned QC testing for pre-marketing applications. However, the laboratories were not always given the relevant dossiers, manufacturer's reference materials and validated methods.

3.9 Market surveillance (product quality monitoring, pharmacovigilance, control of promotion and advertising)

Product quality monitoring

Substandard pharmaceuticals may circulate in the market if good practices in manufacturing, distribution and storage are not adhered to.

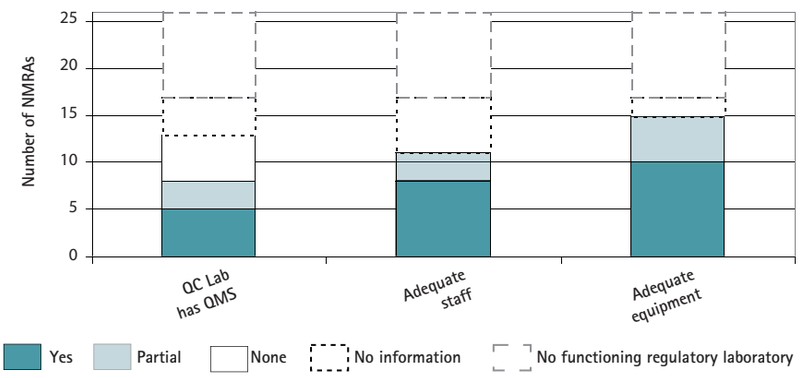
In addition, counterfeiting – the production and distribution of medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source - is becoming an increasing problem. It requires a coordinated response from different sectors both at country level and internationally [25].

In both cases, the deficient products pose a risk for individual and public health.

A risk-based system of inspections and sampling should be in place to monitor the quality of pharmaceutical products on the market. Manufacturers should be obliged to report complaints and quality problems to the NMRA. An effective recall procedure should be in place to remove defective products from the market.

The NMRA should coordinate an anti-counterfeiting programme with all concerned parties, including industry, customs, police and any other stakeholders involved in trade or distribution of pharmaceuticals.

FIGURE 8: QUALITY CONTROL TESTING



KEY FINDINGS (SEE ANNEX 9 FOR DETAILS)

– Fourteen of 26 NMRAs (54%) lacked a quality monitoring programme altogether; 7 tested samples in case of complaints or in the framework of specific programmes, and only 5 (19%) had a systematic approach.

– Twenty of 26 NMRAs (77%) lacked a written procedure to organize an effective recall, of the existing six procedures three needed clarification. Five reports[21] noted the lack of batch traceability needed to recall products. This finding is consistent with the general absence of published GDP guidelines mentioned in Section 4.5.

– Anti-counterfeiting measures included inspections and surveillance in five countries and awareness programmes in three. No country had a specific, comprehensive programme in place at the time of the visits.

Pharmacovigilance (monitoring of adverse reactions to medicines)

Pre-marketing clinical trials are usually conducted on a small numbers of volunteers, who may not always be representative of the target population for whom the medicine is intended. Not all adverse reactions can be anticipated from these studies.

NMRAs should implement a system to monitor adverse events. For this to be effective, there must be a high probability for adverse events to be identified and reported, reports must be reviewed and validated by experts, results must be fed back, and appropriate regulatory action must be taken [8].

21 Countries 09, 14, 18, 20; Country 25 (no traceability of free samples distributed to patients and doctors)

KEY FINDINGS (SEE ANNEX 9 FOR DETAILS)

+ Eight of 26 countries collected reports on adverse events, with three of the programmes being sufficiently established to contribute a sizeable number of results. Seven of the 8 countries were members of the WHO Programme for International Drug Monitoring (see http://www.who-umc.org/).

+ Where it existed, pharmacovigilance was generally not well integrated with other regulatory activities or with clinical surveillance measures implemented by specific national or NGO treatment programmes.

Control of medicine promotion and advertising, provision of drug information

Information propagated through promotion and advertising can significantly influence the way in which medicines are prescribed by health professionals and used by consumers. Inaccurate and misleading information therefore poses a health risk [8].

NMRAs should control promotion and advertising to ensure that any claims made correspond to the approved summary of product characteristics (SPC). They should also provide independent information on medicines to the public and health professionals [1].

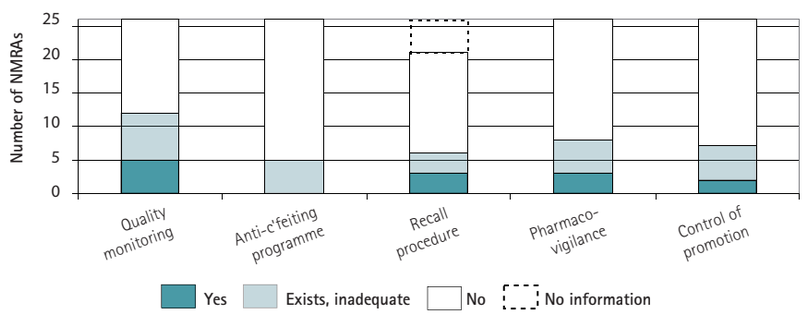
KEY FINDINGS (SEE ANNEX 9 FOR DETAILS)

+ Most countries had some legal provisions for the control of medicines promotion. Seven of 26 countries (27%) controlled pharmaceutical promotion to varying extents.

– In 19 countries (73%) there was no control of promotion and advertising in practice, meaning that even if the regulations were in place, they were not implemented.

– At least 13 NMRAs did not provide any independent medicines information to the public.

FIGURE 9: MARKET CONTROL MECHANISMS



3.10 Oversight of clinical trials

Clinical trials are an essential component of pharmaceutical research and development. They serve to establish the safety and efficacy of new medicines, and to develop new treatment uses of well known medicines. Clinical trials also include *in vivo* bioequivalence studies carried out with generic medicines to establish their therapeutic interchangeability with originator products. In all these types of studies the ethical rights and the safety of trial subjects must be protected, and the methodology must be designed in such a way as to arrive at useful, scientifically valid results.

NMRAs should control clinical trials jointly with external bodies such as national or institutional ethics committees.

Trials should conform with ethical principles for medical research involving human subjects (the Declaration of Helsinki [26]). Guidelines by the Council of International Organization of Medical Sciences (CIOMS)[22] provide valuable additional information on research ethics.

WHO guidelines for GCP [27] and GLP [23] should be followed. GMP of investigational products should be verified. Other more specific guidelines on clinical research may apply.

Trials should be monitored for compliance with all applicable guidelines. Investigators should be required to report on the outcomes promptly, including any serious adverse events encountered.

22 www.cioms.ch

KEY FINDINGS (SEE FIGURE 10 AND ANNEX 10 FOR DETAILS)

+ In 18 of 26 countries (69%) clinical trials were controlled to some extent, mostly with regard to ethical aspects.

– Where ethics committees were involved, NMRAs retained little or no control due to lack of capacity, unclear assignment of responsibilities or non-representation in the relevant committees.

– Adherence to GLP and GCP was not a requirement in 22 countries (85%); detailed GCP guidelines were found in only two countries (8%).

– Eight reports mentioned the absence of import controls and GMP requirements for investigational products.

– Only four country reports mentioned that inspections of clinical trials were being conducted.

4. Conclusions

The countries included in this report had legal provisions for most essential aspects of medicines control. However, their regulatory systems presented some critical weaknesses. The legal framework had evolved over time, resulting in a fragmentation of responsibilities with gaps and grey areas, and a multitude of provisions which were difficult to implement. Many NMRAs had little power and autonomy, and oversaw a limited range of regulatory functions with little accountability or managerial commitment. In almost all countries visited, lack of sustainable funding restricted the regulatory operations. Virtually all NMRAs suffered from staff shortages. For the most part, assessors and inspectors were not at the level of current scientific and technical expertise needed for their regulatory tasks. Regulatory requirements and processes were not in line with recommended WHO standards.

As a result, medicines regulation was not carried out to the full extent required to ensure the quality, efficacy and safety of medicines in African countries. The findings confirm the results of a 2004 questionnaire survey conducted by WHO in 38 African member states, which found that 90% of countries did not provide or enforce adequate regulatory functions [28].

Despite the universally scarce resources and the health workforce crisis experienced throughout sub-Saharan Africa [29], the efficiency of medicines control varied among countries, showing that political commitment at national level can make a difference.

On the positive side, it was noted that many countries were committed to improve their medicines regulatory capacity: Reviews of the systems were invited, and regulatory structures were being adapted. However, in many cases, the transformation processes created new administrative hurdles which complicated effective decision-making, management and release of funding.

The follow-up assessments conducted in four countries showed that progress in specific aspects was achievable. However, the improvements were partial, and were not sufficient to build sound, well-resourced national medicines regulatory systems.

The way forward should be towards effective implementation of medicines control in practice. Political commitment and substantial human and financial resources will be needed for this purpose. Countries will need to take concerted action if they are to expand access to medicines of assured quality for their populations. The following approaches will be useful to build regulatory capacity in Africa:

- Encourage and assist WHO Member States to regularly assess their own regulatory systems in a standardized way. The WHO assessment tool [4] and the accompanying guidance [5] have been developed for this purpose.
- Consider mechanisms to share the outcomes of regulatory assessments.
- Work towards effective implementation of all essential regulatory functions under the umbrella of NMRAs.
- Continuously adapt and update the legal framework for medicines regulation in accordance with internationally recognized norms, standards and best practices.
- Encourage WHO Member States to grant their NMRAs an adequate organizational structure, sufficient autonomy and sustainable resources to enable them to carry out their operations.
- Provide specific, relevant training for assessors, inspectors and other technical staff, in line with current technical recommendations and good practices.

Annexes

ANNEX 1: Geographical, socio-economic and pharmaceutical indicators

Geographic African region[23] / Country	Date of visit	Population (million, 2007) [6]	*Area (km²)*	Life expectancy at birth (years, 2007)	Per capita total expenditure on health at average exchange rate (US$, 2006)	External resources for health as % of total expend. on health (2006)	Out-Of-Pocket expenditure as % of total expend. on health (2006)[24]	Pharmacists	Manufacturers	Distributors	Retail outlets ("Shops" = outlets not under the supervision of a pharmacist)
EAST		345.615									
Burundi	May 2008	8.508	*27 835*	49	$10	48	52	85	*2*	*15*	146
Djibouti	Jul 2007	0.833	*23 200*	56	$63	30	26		1	1 public +pharmacies	9, also acting as distributors
Ethiopia	May 2003	83.099	*1 133 880*	57	$7	43	33	492	13	50	193 (Addis Ababa) +outlets elsewhere
Kenya	Jan 2006	37.538	*582 646*	54	$29	15	42	2775 [29]	**45 [29]**	212 [29]	1700 [29]
Malawi	Jan 2006	13.925	*118 484*	50	$21	60	9	39	4	1 public, a number of private and NGO	26
Mozambique	Feb 2007	21.397	*799 380*	48	$16	60	12		1	45 (incl. 11 active)	229 +shops selling OTC medicines
Rwanda	April 2007	9.725	*26 338*	50	$33	52	22	150	1 public (2 plants)	35 private, +public sector	49 +200 shops
Sudan	2006, Sep 2008	38.560	*2 500 000*	58	$37	7	63	5890 [29]	**24**	296; 1 public, supplies some private outlets	1477 private >5300 public facilities
Uganda	Jun 2009	30.884	*241 038*	48	$24	31	38	300 [29]	17	85	400 private
United Rep. of Tanzania	Jun 2003	40.454	*945 985*	52	$23	44	23	Approx. 650	7+1 small-scale	175 (incl. 40 importers)	349 pharmacies +4000 outlets
Zambia	Mar 2006	11.922	*752 614*	46	$58	38	26		8	63	40
Total	(East):	296.845	(86%)								
SOUTH		55.682									
Botswana	Feb 2007	1.882	*581 370*	56	$379	6	6				
South Africa	Sep 2002	48.577	*1 219 090*	54	$425	1	11	Approx. 10000 [30]	**94 local +international sites**	399	2800, 373 private hospitals, 1800 industrial clinics
Total	(South):	50.459	(91%)								

23 Source of classification into geographic regions: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2009), World Population Prospects: The 2008 Revision, http://unstats.un.org/unsd/methods/m49/m49regin.htm#africa. Sudan as the only country of the North region has been included in the East region.

24 Calculated as: Private expenditure on health as proportion of total expenditure on health × Out-of-Pocket expenditure as proportion of private expenditure on health

24 Calculated as: Private expenditure on health as proportion of total expenditure on health × Out-of-Pocket expenditure as proportion of private expenditure on health

Geographic African region[23] / Country	Date of visit	Population (million, 2007) [6]	*Area (km²)*	Life expectancy at birth (years, 2007)	Per capita total expenditure on health at average exchange rate (US$, 2006)	External resources for health as % of total expend. on health (2006)	Out-Of-Pocket expenditure as % of total expend. on health (2006)[24]	Pharmacists	Manufacturers	Distributors	Retail outlets ("Shops" = outlets not under the supervision of a pharmacist)
MIDDLE		119.097									
Angola	Nov/Dec 2003	17.024	*1 246 700*	53	$71	7	13	Approx. 55	3		281 (capital) +unknown number in other regions
Cameroon	Sep 2006	18.549	*475 650*	52	$45	8	75	900	6 private	15	350
Chad	Sep 2007	10.781	*1 284 000*	46	$29	18	44	47	None	6	47+unknown number of stockists
DRC	Feb 2008	62.636	*2 345 409*	52	$10	52	40	1300	**22**	17 public sector; *79 importers*	*49 licensed +approx. 5000 unlicensed*
Gabon	May 2008	1.331	*267 667*	59	$351	2	27	63 [31]	*2*	*3 importers*	67 +161 shops [31]
Total	(Middle):	110.321	(93%)								
WEST		286.221									
Benin	May 2009	9.033	*112 620*	57	$26	21	47	235	2	5	149; 245 shops, 725 public sector outlets
Burkina Faso	Oct 2006	14.784	*274 200*	49	$27	33	39	245	5 (incl. alcohol, trad med)	6	155
Cote d'Ivoire	Sep 2006	19.262	*322 463*	54	$35	8	67	933	8 (incl. 3 inactive)	3	605 +1378
Ghana	July 2004	23.478	*239 450*	57	$33	23	51	1798 [29]	**29**	(Regulated by Council – no data recorded during visit to NMRA)	1186 operated by pharmacists; 9814 other licensed outlets [32]
Mali	2003; May 2007	12.337	*1 240 000*	49	$31	18	50	550	2	17 private; public: 1 central, 13 regional	265 +124 stores +595 community-owned
Niger	April 2009	14.226	*1 267 000*	51	$16	34	44	200	1	12 private; public: 1 central, 3 depots	Public: 44, 9 hospitals Private: 79, 89 shops
Nigeria	2004; Jan 2007	148.093	*923 768*	49	$33	6	64	6748 [29]	**132; approx. 60 registered**	995	1604 +many shops
Senegal	2003; May 2007	12.379	*196 722*	59	$44	12	33	908 [31]	4	4 private; public: 1 central, 6 regional	620 +100 shops +many illicit outlets
Total	(West):	253.592	(89%)								
Grand Total:	711.217 of 806.615 (88%)										

Source: WHO. World Health Statistics 2009, unless otherwise stated . **Source of classification into subregions:** Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2009). World Population Prospects: The 2008 Revision. http://unstats.un.org/unsd/methods/m49/m49regin.htm#africa. Sudan as the only country of the North region has been included in the East region.

ANNEX 2: Organizational structure and implementation of regulatory functions

● = NMRA; ○ another body, ○○ = two other bodies, ●○ = NMRA and another body, ●○○ = NMRA and two other bodies, ✖= not assigned to a specific body; shaded: operational at the time of the visit

Country	Year of enabling Act	Authority and legal form: A: Government Department B: Autonomous body C: Parastatal agency		Marketing authorization (see also 3.4)	Licensing & import control (see also 3.5)	Inspection (see also 3.7)	Quality control (see also 3.8)	Pharmaco-vigilance (see also 3.9)	Control of promotion (see also 3.9)	Control of clinical trials (see also 3.10)	Vet meds	Trad./ herbal meds
EAST												
02	1978	Autonomous body, **(later semi-autonomous agency)**	B	●	●	●	●	●	●	●	Yes	Yes
03	1988	Semi-autonomous parastatal Board	C	○ Minister on NMRA advice	●	●	●	✖	●	●	Yes	No
04	1999	Parastatal, autonomous body +advis. board (no technical committees)	C	●	●○	●	●	●	●	●	Yes	Yes
06	1999	Department within MoH, transitional **(awaiting transformation into agency)**	A	●	●	●	✖	●	●	✖	Yes	No
07	1998	Delegated to Pharm Dept MoH **(NMRA never formally established)**	A	●	●○	●○	○	○	●	○	Other auth.	No
09	1982	Department within MoH **(not officially constituted)**	A	●	○	○	✖	✖	✖	○	Other auth.	Yes
10	2001	Department within MoH **(NMRA proposed, not yet established)**	A	✖	✖	○	✖	✖	✖	✖	No	No
15	1963	Department and Secretariat in MoH on behalf of autonomous Board	A	●	●○	●	●	●	●	●○	Other auth.	Yes regist
16	2004	Autonomous board **(not yet approved at time of visit)**	B	●	●	●	●	✖	●	●	Yes	Yes
20	1957	Board as body corporate (all technical staff seconded by MoH)	B	●	●○○	●○	○	●	●	○	Yes	No
26	1952	Body corporate (Board and Secretariat)	B	●	●○	●	●	●	●	●○	Yes	Yes regist
SOUTH												
11	1965	Agency, supported by MoH (+professional council)	C	●	●○	●○	✖	●	●○	●○	Yes	Yes
21	1992	Medicines regulatory department within MoH (functions and responsibilities not clearly stated in legislation)	A	●	●○	●	○	●	●	○●	No	No

Country	Year of enabling Act	Authority and legal form: A: Government Department B: Autonomous body C: Parastatal agency		Marketing authorization (see also 3.4)	Licensing & import control (see also 3.5)	Inspection (see also 3.7)	Quality control (see also 3.8)	Pharmaco-vigilance (see also 3.9)	Control of promotion (see also 3.9)	Control of clinical trials (see also 3.10)	Vet meds	Trad./ herbal meds
MIDDLE												
05	1992	Department of MoH **(proposed, not yet implemented)**	A	●	○○	○	×	●	×	×	Other	No
08	1990	Department within MoH	A	●	●○○	○	○○	●	●	○○	No	Yes regist
12	1933[25] 1952, 1982	Department within MoH	A	●	●○	●	×	●	●○	×	Yes (no regul)	Yes regist
17	2000	Department within MoH	A	●	●	●	×	●	●	●	Yes	Yes
25	1961	Department within MoH	A	●	●○○	○	×	●	●	○	Yes	Yes regist
WEST												
01	1994	Department within MoH	A	●	●	○	○	×	●	○	No	Yes regist
13	2006	Department within MoH	A	●	○	○●	○	●	○	○	No	No
14	1962, 1994	Department within MoH	A	●	●	●○	○	●	●	●	Yes	Yes
18	1984	Department within MoH	A	●	●	○	○	●	×	●○○	Yes	Yes regist
19	1992	Board under control of MoH (+Prof. council +Standards board)	C	●	●○	●○	●	○	●	●	Yes	Yes regist
22	1995	Department within Ministry of Public Health	A	●	●○	●○	○	●	○	○	Yes	Yes regist
23	1954	Department within MoH	A	●	●	●	○	●	●	○	Yes	Yes regist
24	1993	Parastatal agency (+professional council +enforcement agency)	C	●	○	●○	●	○	●	●	Yes	Yes regist

25 1933 legislation on the practice of pharmacy remains the basic legislative framework; NMRA was constituted by legislation of 1982.

ANNEX 3: Organizational structure and management

Region / Country	Type[26]	Funding: Sources	Retained	Adequate, sustained	Quality Management System	Staff (technical +admin)	Human resource (HR) management	Code of conduct / interests	Information, consultation with stakeholders	Web-site[27]	Gaps / remarks
EAST											
02	B	Public, donor, fees	Yes	No	Being drafted	35 +16 Insufficient	Structure not documented. No HR development plan	No	Some reports (except financial)	**	Good consultation/ cooperation nationally
03	C	Public, fees, commission	Yes	No	No	Board: 7 5 committees	No HR dev.plan. Gaps in job descriptions	No	Some, website needs updating	Yes ***	Heavy reliance on donor/project finance
04	C	Public, fees to gov., partners	No	No		58 +55 Insufficient	Planning, job descriptions, but no HR dev. plan	Not specific	Reports available through Parliament	**	No technical committees to support Board
06	A	Public, donor	Yes (proposed)	No	No	Insufficient	No own recruiting. Training plan exists	No	Info not publicly available	**	Underresourced transitional organization
07	A	Public, fees to government, donor	No	No	No	7 +3 Insufficient	Job descriptions, no own recruiting	No	Very little; website of MoH not used	No	Low salaries; inadequate buildings
09	A	Public, fees to government	No	No	No	7 technical Insufficient	No HR dev plan, no job descriptions	No	Information not generally shared	No	No autonomy, inadequate buildings
10	A	Fees, import levies (proposed)	Yes	n/a	(NMRA not established)	2	n/a	n/a	n/a	n/a	(No regulatory authority)
15	A	Public, fees, donor	Not yet (agreed)	No	**Not comprehensive**	35 (Board) +Secr.	No own recruitment. Unclear job descriptions; some training planned	**Yes** for external, +oath-taking	Some consultation, no info on decisions	Yes	Policy centralized but regulatory functions decentralized
16	B	Public, fees	Yes	No	No	(Transitional) Insufficient	No strat. plan; lack of staff to manage finance	No	No website	No	Critical position of Dir. General not filled
20	B	Fees only	Yes	No	? (Not for inspections)	Tech staff seconded by MoH	No own recruiting: no HR management systems	No	Outdated website, difficult to access	Yes	Registrar in charge of procurement
26	B	Public (20 Board members only); fees	Yes	No	**Not implemented officially**	Secretariat: 68+55 Adequate	Job descriptions (2001); training (not systematic)	**Yes** (not for external)	Website: some links to forms not working	Yes	Secretariat should be given responsibility for daily functioning
SOUTH											
11	C	Public, fees to government	No. Fees-only system proposed	No		22 members, 110 MoH 146 external	No HR dev plan for MoH staff, unclear job descriptions	**Yes** for external, gen code for MoH	Informal consultation Administrative info available	Yes	No own staff - external part-time experts and MoH staff
21	A	Public, fees to government	No	No	No	6 +zero Insufficient	Inadequate. No own recruiting. High turnover	No	MoH website, guidelines not posted	Yes	Lack of staff and funding a major problem

Region / Country	Type[26]	Funding: Sources	Retained	Adequate, sustained	Quality Management System	Staff (technical +admin)	Human resource (HR) management	Code of conduct / interests	Information, consultation with stakeholders	Web-site[27]	Gaps / remarks
MIDDLE											
05	A	Public, donor, fees proposed	No	No	(NMRA not established)	14 +16 Insufficient	No HR development plan	No (general only)	Little information-sharing	No	Structure not yet functional
08	A	Public, fees to government	Redistribu-tion 45%	No		22 technical Need training	No HR development plan	No	NMRA not using Min. Public Health website	No	Government funding not always released
12	A	Public; fees, donations	Redistribu-tion 25%	No	No	7 technical Insufficient	No HR development plan. No legal support	No	Consultation on new regulations / policies	No	Delayed release of funds (except salaries)
17	A	Public, donor	Redistribu-tion 70%	No	No	7 technical Insufficient	No HR development plan. No legal support	No	Consultation on new legislation	No	Tasks of technical committee not defined
25	A	Public, fees	Redistribu-tion 40%	No	No	*13 technical* Insufficient	No organigram, job descriptions or HR dev plan	No	Isolated initiatives (MA/industry)	No	Internal technical committee, no rules
WEST											
01	A	Public, donor	No	No		27 +6 Need training	No HR development plan	No	Some consultation (prof. associations)	**	Funding not released in time. No internet.
13	A	Public, fees, donor	Yes, special account	No	No	5 +10 Insufficient	No organigram or job descriptions, no HR development plan	No	Limited information available; little visi-bility. Action plan for good governance	No	Director is also head of tender board
14	A	Public	No detailed plan	No		15 +10 Need training	Five-year plan, no details on funding		Some consultation (prof. associations)	No	Very limited budget
18	A	Public, fees to government	No	No	Being drafted	13 technical Insufficient	No HR development plan, no legal support	No	Some consultation. Website needs regular updates	Yes	No procedures established for technical committees
19	C	Public, fees (no legal basis), donor	Yes, special account	? Not backed by law	No	61 Insufficient	No HR development plan, training conducted ad hoc	Partial (confidentiality only)	Insufficient consul-tation. Website under construction	**	Three units located in different places. Board not appointed.
22	A	Public, fees, donor	Yes, except licensing fees	No	No	11 technical Insufficient	No specific training, no development plan. No organigram or job descript.	No	Action plan, but no specific measures to promote transparency	No	Inflexible funding allocation. Lack of basic equipment (copy machines, telephone exchange)
23	A	Public, fees to government	No	No	**Being initiated**	9 technical Insufficient	No HR dev plan No legal support, eight vacant posts	No	Profess. council representation. Web-site not maintained.	Yes	No procedures established for technical committees
24	C	Public, fees, donor	Yes	No	**Yes, for admin. processes**	Insufficient	No HR dev plan, No job descript. for key staff	General (Civ. Serv.)	Site not updated. Little consultation	Yes	Poor infrastructure and maintenance

26 A: Government Department , B: Board/Council/Body corporate, C: parastatal agency.
27 ** = Website introduced after visit [11] *** Website no longer found in 2009

ANNEX 4: Marketing authorization

+= existing, ± = existing but inadequate, – = not existing

Region / Country	Adequate legal basis	Guidance for applicants	SOP for assessment	Advisory committee	External assessors	Full time assessors	Secure filing space	Computerized system	List of approved products, incl. SPC	Recognition of stringent MRAs' decisions	Gaps / remarks
EAST											
02	+	±Inadequate	±Not adequate	Technical committee	Limited	7 Insufficient	±	±Database, SIAMED (for some parts)	List without SPC or pack sizes	No	Donations exempt
03	+Minister=licensing authority	±Checklists	±Admin only	Yes, but no time/ capacity	No	4 Insufficient	±	– None	List not updated, no SPC	No	**Screening only done** Broad exemptions
04	+	±Not comprehensive	? Report format exists	Internal, no technical committees	No	10 Insufficient	±	±Stand-alone database	List not published, SPC not assessed	No	Local prodEt publ. sector exempt. No specific requirements for vaccines
06	+	– None	– None	No	No	Insufficient	±	– None	List not published	No	**MA granted without dossier evaluation**
07	+	±Not comprehens. No guidance on BE, stability	– None	Not operational	**Stopped** 1 year before visit, no funds	Insufficient	±	±Stand-alone database	List outdated, not published	US-FDA, WHO-PQ, EU	Exemptions f.orphan products, public sector imports **Assessments stopped**
09	±Requirements not specified	±Not detailed, outdated	– None	Not operational	Transitional, **inactive**	3 Insufficient	±	– None	*List exists, but no website*	CPP requested	**No ongoing evaluation (no tech. capacity)**
10	– (Proposed, no details)	---n/a---	---n/a---	---n/a---	---n/a---	n/a	n/a	---n/a---	---n/a---	---n/a---	**Regulatory system not yet established**
15	+	+Detailed info on format/ content	+Written SOPs	Yes	Yes	Insufficient	±	±networked MIS d'base	List without SPC		Superfluous step of "pre-registration" of generics and essential meds
16	±Act, but no regulations	±Not updated	–None	Not operational	Yes	Insufficient	±	±Database; 1 878 pending applications	Limited info, not updated	Not formal	No specific requirements for vaccines

Region / Country	Adequate legal basis	Guidance for applicants	SOP for assessment	Advisory committee	External assessors	Full time assessors	Secure filing space	Computerized system	List of approved products, incl. SPC	Recognition of stringent MRAs' decisions	Gaps / remarks
20	+	±Few g'lines, outdated (1981)	–None	Yes	Exclusively	Insufficient	±	–None	Not published *(2009: web)*	No	No provisions f. vaccines; no guidance on variations
26	±No detailed legal instrument	+Technical info not consistently updated	±Not for entire process	Yes	No	6	±	±SIAMED +other database	Not published *(2009: web)*	CPP reviewed, not required	All oral solid dose anti-infectives exempt from bioequivalence studies
SOUTH											
11	+	+Detailed info on format/ content	±Checklist	11 expert committees	Exclusively, Qualified experts	None Insufficient	+	±Stand-alone databases	List without SPC	Yes, defined list of MRAs	Remuneration issues, delays. Assessments take 12-24 months
21	+	±Not comprehensive E.g no guideline for renewal	–None	Yes	Yes	All participate Insufficient	±	–None	Outdated list	Decisions from other NMRAs requested	Process can take 5 years Backlog of approx. 1000 applications
MIDDLE											
05	±Act, but no regulations	–None	–None	No	No	Insufficient	±	–None	No	No	**System not yet operational.** Donations exempt
08	+		+Validated SOPs	7 specialized 1 national	Yes	4 Sufficient	±	+SIAMED		CPP requested	No procedure for veterinary products
12	+		–None	Not for MA specifically	No	3 Insufficient	±	–None			No regulations for vaccines, reagents, vet meds
17	+		±Admin only	Yes	Yes	2 Insufficient	+	+SIAMED			No procedures for technical evaluation
25	+Brief description of required dossier components	±Not detailed, outdated	–None	Unofficial	No	14 Insufficient	±	±GIRAPH, not optimal	Yes; SPC not included in registration certificate	CPP requested	**Mainly administrative review.** Few requirements for generics

Region / Country	Adequate legal basis	Guidance for applicants	SOP for assessment	Advisory committee	External assessors	Full time assessors	Secure filing space	Computerized system	List of approved products, incl. SPC	Recognition of stringent MRAs' decisions	Gaps / remarks
WEST											
01	+Brief outline	±Brief, no technical guidance	+Manual & guide	Yes	Yes	4 Sufficient	+	+SIAMED		CPP requested	Vaccines not regulated by MRA
13	±Incomplete and outdated regulations	±Not sufficiently detailed, outdated	±Admin only	Yes (no specific expertise)	Yes, and QC lab staff	3 Insufficient	±	+SIAMED	SPC not included in registration certificate	No	**Mainly administrative review.** Some donations and investigational products exempt
14	±Dating from 1994	±Some	±Informal internal doc	Yes; no specialized committees	Yes (few)	4 Insufficient	±	–Manual only; major problem	List not published, SPC not assessed		Renewal of MA not followed up by NMRA or applicants
18	+	±Regulation and Circular	±Admin only	Yes	Yes	Insufficient	+	+SIAMED (backlog)	*2009: List on website (no SPC)*	No	No procedures for technical evaluation
19	±Incomplete regulations	±Not comprehensive	±Some	Informal	Yes	10 Insufficient	±	–None	*Dec 09: list of Oct 08 on website, no SPC*	No	Lack of assessors a major problem; procedures need improvement
22	+	±Not sufficiently detailed, outdated	±Admin only	Yes (few meetings, delays)	No	*1* Insufficient	±	±Excel, not networked	Registration certif. has limited information	No	**Mainly administrative review.** Lack of specific skills and information
23	+	±Circular describing the process	±Admin only	National committee	Yes	2 Insufficient	±	+SIAMED		No	Technical procedures need improvement
24	+	? Guidance has been published	±Admin only	No	Various internal committees	Insufficient	±	±Database networked within dept.	List gazetted, web not updated, no SPC	Yes, country of origin	Donations, orphan medicines exempt

ANNEX 5: Licensing of activities

● = NMRA; ○ another body, ○○ = two other bodies, ●○ = NMRA and another body, ●○○ = NMRA and two other bodies, ✖= not assigned to a specific body

Region Country	Authority	Description, **gaps**
EAST		
02	●	Approval to manufacture is granted on a product-by-product basis; manufacturers are supported to meet minimum GMP standards.
03	●	Control by two different committees (one for manufacturers / distributors, another for retail), **some renewals without inspections.** Some facilities operate under locum pharmacists for months. **List of licensed businesses not readily available**
04	●○	NMRA certifies competence **(public sector exempt)**, license by Ministry of Trade. GMP not in line with WHO standards. Retail: **regional control but reporting system not finalized.** Poor cooperation with other national enforcement agencies (customs, police).
06	●	Licence required by law, but regulations exist for **pharmacies/depots only**
07	●○	National and Regional MoH (**no official delegation** to the latter, no regular reporting system). Licences have no validity date. **Public hospital pharmacies exempt.**
09	○	Ministry of Public Health on Inspectorate's advice; **few requirements for manufacturers and distributors**
10	✖	(Retailers inspected by Public Health inspector)
15	●○	Scattered responsibilities: Dep2,3,6 (local manufacturers), Dep6 (foreign manufacturers) Dep3+regional authorities (retail)
16	●	**Regulations on controls of distribution channels not enacted**
20	●○○	NMRA & QC Lab (for manufacturers & retail) - **conflicting responsibilities; unclear exemptions** (e.g. hospital pharmacies). MoH Inspectorate (for distributors).
26	●○	NMRA (manufacturers & distributors). MoH licenses private pharmacies, **no rules for public hospital pharmacies**
SOUTH		
11	●○	NMRA (in connection with MA) Professional council (for establishments)
21	●○	MoH (licences issued by Min. Trade) **Public health facilities and dispensing doctors not inspected**
MIDDLE		
05	○○	Control by National Health Inspectorate +Ministry of Commerce, **but no enabling regulations** on good practices for manufacturing, sale and dispensing
08	●○○	NMRA (preparation), Ministry Pub Health (retailers). Professional council (manufacturers, distributors, importers)
12	●○	Control by three different departments, depending on product type **Some pharmacies have municipal approval only**
17	●	NMRA (for manufacturers, distributors, retailers). Professional council levies fee for retailers, **no control of medicine shops**
25	●○○	MoH, on advice of NMRA and Health inspectorate. **Requirements not defined**
WEST		
01	●	Control by two different departments, depending on product type. **No GMP inspections**
13	○	Approval by Minister of Health on advice of professional council and technical committee. **Inspection** only after licence is granted. **GDP not required for distributors. Some unlicensed facilities (e.g. faith-based)**
14	●	Control by two different departments (one for manufacturers, **also tasked to promote local industry**, another for distributors and retailers). **Inadequate information management.**
18	●	**No operating procedures**
19	●○	NMRA +inspectors from other departments (for manufacturers) Professional Council **(**for distributors, retailers)
22	○	MoH on advice of NMRA, Inspectorate, Professional Councils. **No specific regulations** for various types of establishments. **GSP required but not published. Some unlicensed distributors.**
23	●	No SOPs in place for licensing
24	○	Pharmaceutical activities controlled by professional council **(no licensing for manufacturers of investigational products)**

ANNEX 6: Import control

Region / Country	Description, **gaps**
EAST	
02	Control of APIs and FPPs by reviewing pro-forma invoices
03	Import: **Not enforced, no inspection system**; products for **specific patients exempt. Export: no legal requirements**
04	Specific provisions on import /export exist **for narcotics only.** Import based on national medicines list or written request by a doctor
06	Licensed establishments can import pharmaceuticals **without any requirements**
07	**MA not required for public sector imports; no actual inspection**
09	NMRA, based on MA **(no list of licensed distributors)**. Private company controls import acts and prepares documentation.
10	Import control not yet implemented
15	MA needed, but **no list of exempt products**
16	Legal basis but no regulations enacted
20	No written guidelines for import / export licences; list of licensed importers and exporters not readily available
26	Annual licence & verification of each import. Less control for **unregistered products**
SOUTH	
11	Imported products need MA; NMRA reviews CoAs
21	Imported/exported products need MA. **Products imported by Central Medical Stores and donated drugs are exempted** from registration

Region / Country	Description, **gaps**
MIDDLE	
05	**No specific requirements to control import of APIs, no certification of exports**
08	
12	Approx. 90% of products imported.
17	100% of products imported. Since 2007 importation only through licensed wholesalers, but **not controlled in practice**
25	Imported products need MA, but some exceptions. NMRA authorizes imports for specific treatment needs without official delegation and **without defined procedure. Lack of regulation for donations. Export not regulated**
WEST	
01	98% of medicines imported. **Regulations to be adopted**
13	**Wide range of authorized importers; no system to keep track of product status (MA), regulations not adequate to control donations**
14	Based on MA, but **no computerized lists**
18	**Lack of control for investigational products**
19	Importers licensed by professional council; NMRA **has no legal basis for inspection**
22	Need approval by MoH on advice of NMRA. **No system to verify lot numbers, authorized importers, registered products. No active collaboration with customs**
23	MA needed, but **exemptions unclear**
24	Only licensed establishments can import. NRA screens documents, some inspections/ testing

ANNEX 7: Inspections

● = NMRA; ○ another body, ●○ = NMRA and another body
+= existing; ± = existing but inadequate, –= not existing

Region / Country	Authority / ies in charge		Legal basis	GMP required	Published GMP guidelines	Published GDP guidelines	SOP for inspection	QMS	Inspectors	Inspectors	Logistics	Main gaps / remarks
EAST												
02	●	+regional officers	+	Yes	±Not to WHO standards	None	±Checklist	–	10 +regional	+	±	Poor coordination, inexperienced inspectors
03	●		+	Being phased in	–None		±Checklist, outdated	–	2 +4 assistants	±	±	Pharmacists from distribution channels do inspections: conflict of interest
04	●	+Regional branches	±No specif. provisions to control activities	No	±Not to WHO standards	None	±Checklist	–	10 ph'cists (central level)	±	±	Lack of staff, training, experience and resources
06	●		+	Yes (no regulations)	–None	None	–None	–	2	±	±	Lack of staff and resources, **not functional**
07	●○	+Regional MoH inofficial)	+	Yes	–None	None	±Checklist	–	3	±	±	Lack of transport a major problem
09	○	Public health inspectorate	+	No	–None	None	±Checklist	–	*6*	±	±	Severe lack of qualified staff Delays in release of funds
10	○	Health inspector	±Pharmacies only	n/a	n/a			n/a	1	±	±	Inspections of pharmacies were the only regulatory function
15	●	+Regional +QCL staff	+	Yes	±Worked out by local committee				16	±	±	Large differences in stringency between regions
16	●	+Regional	±No regulations	Not for MA	±Not to WHO standards		–None	–	6 +17 part time	±	±	Staff, funds and GMP training needed. No routine inspections
20	●○	+MoH +QC staff	+	No	+WHO text, nat. draft unfinished	None	–None	–	4	±	±	Few inspections. No plan for follow-up
26	●	+Regional staff	+	No	–Unpublished draft modeled on PIC/S	None	±Checklist	–	33 +65 regional	+	+	Hospital pharmacies not regularly inspected
SOUTH												
11	●○	+Professional council	+	Yes	+	Yes	±Outdated	– To be set up	NMRA: 10 Council: 34 part-time	+	+	NMRA not in charge; Profess. council makes final decision based on GMP inspection reports, and inspects distribution chain
21	●		–(Function not mentioned in Act)	Yes	–None	None	±Checklist	–	No	±	±	Lack of resources, no responsible person. Publ. sector outlets & dispens. doctors not inspected

Region / Country	Authority / ies in charge		Legal basis	GMP required	Published GMP guidelines	Published GDP guidelines	SOP for inspection	QMS	Inspectors	Inspectors	Logistics	Main gaps / remarks
MIDDLE												
05	○	Pub Health inspectorate +regional staff	+	No (proposed for MA)	±Not to WHO standards	None	–None	–	69	+	±	Inspectorate not well equipped. To serve as enforcement arm for proposed NMRA
08	○	MoH inspectorate	+	No	–None	None	–None	–		±	±	Lack of staff and resources, poor coordination with NMRA
12	●	Several NRA departments +regional	±Not specific to types of inspection	No	–None	None	–None	–	24	±	±	Lack of staff and resources; no reports
17	●		±No inspectors' status	No	–None	None	±Checklist	–		+	±	Lack of resources
25	○	Division of Public Health Inspectorate	+	No	–None	None	–None	–		±	±	Lack of staff and resources
WEST												
01	○	Public Health Inspectorate	+	No	±Not to WHO standards	Not to WHO standards	–None	–	2	±	±	Lack of staff and resources, poor coordination with NMRA
13	●○	Inspectors named by Min Pub Health	±Inspectors' powers not well defined	Yes	–None	–None	±Checklist	–	*4* (incl. one from NMRA)	±	±	Reports addressed to Min Pub Health. Annual plan not fulfilled due to lack of inspectors and resources
14	●○	+MoH	±Responsibilities not clear	No	+WHO text	WHO text	–None	–	27; 2 from Ministry of health	±	±	Lack of staff. Affiliation of inspectors unclear
18	○	Health Inspectorate	+	? Not for MA	–None	None	+Yes		10	±	±	Annual plans not met due to lack of staff and resources
19	●○	+Professional Council	+	No	+WHO text	? (Control by Council)	±Not comprehensive	–	6 +from other dep	±	±	Lack of staff and resources. Council lacks resources to carry out its mandate
22	●○	+Health Inspectorate	±Some regulations not published	Yes (regulation not published)	–None	None	–None	–	? None from NMRA	±	±	No legally empowered NMRA inspectors, inspectorate staff not pharmacists
23	●		+	Yes	+	None	+Yes, not validated	–		±	±	Lack of staff; GMP training needed
24	●○	+Professional Council	+	Yes (no regulations)	–None	None	±Checklist	–	*538*	±	±	Overlap of activities (NMRA/Council) – grey areas

ANNEX 8: Quality control

● = NMRA; ○ = another body, ○○ = two other bodies, ✕ = no QC lab;
+= existing, ± = existing but inadequate, –= not existing; -------= no QC lab (not reviewed)

Region / Country		Description of regulatory QC laboratory	Quality management system	Staff (tech+admin)	Equipment & maintenance
EAST					
02	●	NMRA department. Tests pre-marketing samples	+Can be strengthened	+(13 tech.)	+
03	●	Housed at Central Med Stores; mainly tests public. sector imports	–Not functional (some SOPs)	±	±Inadequate
04	●	NMRA department. Tests pre-marketing samples.	–No written system, no SOPs	±(16 tech, lack of skills)	±Lacking some major equipment
06	✕	None. External labs used	-------	-------	-------
07	○	National QC lab. No link with NMRA. Tests public sector imports	±In first stage of implementation	+(20 +6)	+Lack of space/ maintenance
09	✕	External (costly, delays); National Health Institute (not yet set up)	-------	-------	-------
10	✕	(None, NMRA not in place)	-------	-------	-------
15	●	Affiliated without legal basis. Pre-market QC for each batch, not efficient. Lack of funds	+Aspiring to ISO 17025 certificat.	+(33+3)	+Lack of space
16	●	Not operational since 1999; new laboratory proposed	-------	-------	-------
20	○	Autonomous lab, staff seconded by MoH	–Reportedly being developed	? (*11 tech)*	+
26	●	Tests first 3 batches of all local production	+Q Manual and several SOPs	+(12 tech)	+Lack of space
SOUTH					
11	✕	MoH lab/academia/private; Contracting-out discontinued	-------	-------	-------
21	○	Central Medical Stores lab; no legal basis		? (10 tech)	±Basic
MIDDLE					

Region / Country		Description of regulatory QC laboratory	Quality management system	Staff (tech+admin)	Equipment & maintenance
05	×	None; sole manufacturer's lab used	-------	-------	-------
08	○○	Nat.Lab; tests pre-MA samples +Res Centre (poor coordination)		+	
12	×	None, 4 approved labs contracted by Min Pub Health	-------	-------	-------
17	×	None, outside labs used; QC lab to be set up by 2010	-------	-------	-------
25	×	None, external labs used. Study to set up QC lab under way	-------	-------	-------
WEST					
01	○	Nat. Public Health lab. Tests pre-marketing samples		±Lack of skills	±Not optimally used
13	○	National lab; wide range of tasks	–Some SOPs	+(Except for biologicals)	+Lack of space; being rehoused
14	○	National lab, tests samples for MA. Many other functions.	±Being set up, partly functional	+	±Mostly old
18	○	National QC Lab, tests pre-marketing samples	–Will be set up	+(12 tech)	+
19	●	NMRA Lab service	±No responsible person	+	+Lack of space
22	○	National lab	+WHO/ISO17025 standards	+(Except for biologicals)	+Lack of environmental control
23	○	National lab, receives dossiers and tests samples	+Manual/SOPs based on OECD	+(16 tech)	+
24	●	Yes (not reviewed during visit) Tests pre-marketing samples	Not reviewed	Not reviewed	Not reviewed

ANNEX 9: Market surveillance

● = NMRA; ○ = another body, ✖ = not assigned to any official body; += existing, ± = existing but inadequate, –= not existing

Region / Country	Product quality monitoring	QC testing of samples	Anti-counterfeiting programme	NMRA procedure for effective recall	Pharmacovigilance system *=member of WHO Programme f. Int'l Drug Monitoring at time of visit (http://www.who-umc.org/)	Control of promotion	Meds information
EAST							
02	+Samples collected and tested		±Surveillance for counter-feits (to be strengthened)	–None	±* Manual recording, results sent to **WHO-UMC**. 82 reports received in year before visit.	±Not always effective; SPC not available. Med. reps subject to control	+
03	–No PMS system (in preparation)	Few	±Surveillance by inspectors, no specific programme	–Legal provision not implemented	–No system	–Not implemented	–
04	–No PMS system	In case of complaints	–None		±Reports received, lack of experts for assessment.	±Guidelines not finalized; not based on approved product info	+
06	–No PMS system	In case of complaints	–None	–None	–Not established	–No regulations, not operational	–
07	–Not implemented, lack of inspectors and transport	None conducted	–None		±* MoH Centre. Public sector, selected districts. Results sent to **WHO-UMC**. No link with NMRA	–Some legal requirements, but no control in practice	
09	–No PMS system	"If needed"	–None	–None	–No system	–None	–
10	–No PMS system		–None. Unregulated prices fuel the illicit market	–No NMRA	–No system	–None	–
15	+Samples submitted by public stores, UN agencies, NGOs		–None	±Not comprehensive	±* Newly introduced; three reports transmitted to **WHO-UMC**, training under way	–Legal basis exists, responsibility newly assigned within NMRA	
16	–Not operational		–None	+SOP; follow-up during inspections	–Vague legal basis: "monitoring safety". No activity	–Legal basis but not implemented	–
20	±Ad hoc based on feed-back from the market	In case of complaints	–None	–None	–Unit established, no activity *(launched June 2009)*	±Guidelines but no systematic monitoring	
26	+Samples purchased regularly from the market	and minilabs (regional)	±Market surveillance by inspectors	+SOP	±* Vague legal basis. Reporting of adverse events since 2008. Results sent to **WHO-UMC**.	±Ambiguous regulations, unvalidated draft guideline	+
SOUTH							
11	±For public sector tenders; no national system		±Inspections (outlets, ports of entry, post offices)	+Complaints-based only	+* Reporting to **WHO-UMC**, and ARV-specific centre (being set up at time of visit)	+Monitored by Advertising Standards Authority. SPC not available to check claims	+
21	–No PMS system		–None	–None	–No legal basis. No activity, draft guidelines	–Not mentioned in Act, not controlled in practice	

Region / Country	Product quality monitoring	QC testing of samples	Anti-counterfeiting programme	NMRA procedure for effective recall	Pharmacovigilance system *=member of WHO Programme f. Int'l Drug Monitoring at time of visit (http://www.who-umc.org/)	Control of promotion	Meds information
MIDDLE							
05	±Inspectorate will investigate complaints	Suspect samples	–None	–None	–None	–None	–
08	–Lack of inspectors to cover the territory	No (costs)	±Multi-sector plan, national awareness day		–No activity, draft reporting form	–Regulations obsolete, under revision. *Committee not functional*	–
12	–No regulations, organized by distributors	(Importers at own cost)	–None	–Only by distributors, not NMRA	–No activity	–With Ministry of Arts. No regulations, no control in practice	–
17	–No PMS system, few inspections	Suspicious cases only	–None	–None	–Not established	–Regulations exist; *system not operational*	
25	–No PMS system		–None	–None	–Not established, draft reporting form exists	–Information must correspond to MA; not implemented	–
WEST							
01	±45 substances monitored, depending on resources	Lab not involved (cost)	–Awareness programmes		–No system	–No regulations, no control	
13	–QC Laboratory can request samples. No coordinated strategy	Market control main task	–None. Plans to set up a national committee	–None	–Not established; draft reporting form. No link with specific disease programmes	–Approval by Min Public Health (but no regulations); promotion targeted at med. professionals free	–
14	±Weak system		–No official measure	–Admin decision on demand of manufacturer/importer	–No regional reporting structures	±Promotional material reviewed for import permits only; medical samples not controlled	
18	±Collaboration with QC lab; PMS system not comprehensive	In case of suspicion	–Media awareness programmes	±Circular letter – needs more details	–No activity, draft reporting form	–No regulations	–
19	+Samples collected and tested. Lack of inspectors for sampling	Yes	–Grey areas, no coherent measures		+*Nat. pharmacovigilance centre, no link with NMRA. Reporting to **WHO-UMC**	–Not operational	
22	+Samples taken along distribution chain (especially publ. sector)	QC testing of generics	–No coordination between NMRA, customs, police	–None	–No activity; 1 staff member trained. No link with disease programmes	–Min. Pub. Health on advice of committee (not set up). **No control in practice**	–
23	–No PMS system	For nat. programmes	–None	±Needs clarification	–NMRA assisted by committee. Very few reports, no analysis. Not linked to other programmes	+Control takes place	–
24	±Not risk-based, no guidelines or SOPs; NMRA cannot control entire territory		–No specific programme (Task Force exists)	–Power to ask for recall, but no SOP	+* No legal basis. Centre located in NMRA. Results sent to **WHO UMC** and considered in regulatory decisions.	–Not operational	

ANNEX 10: Control of clinical trials

● = under the umbrella of the NMRA; ○ = assured by another body, ✖= no provision in regulatory system

Country	Authority	GCP/GLP required	Inspections	Gaps / remarks
EAST				
02		No	No	One application to date of visit. No guidelines, no technical committee
03		No	No	**No control**; no guidelines for applicants. Lack of capacity and no links with existing ethics committees (whose role in controlling CT was not clear).
04				*National advisory committee assists with ethical evaluation. NMRA lacks capacity.*
06		---	---	**No system**
07	○	No	No	Ethical oversight by Nat. Health Institute. No published guidelines on GCP/GLP, staff not trained. NMRA controls product importation.
09	○	No	No	Authorization by MoH. No import control or GMP for products, no regulations
10		---	---	**No system**
15	○	No	No	NMRA and Nat. Ethics Committee. Two Acts, duplication of responsibilities. No regulations/guidelines. Insufficient expertise within NMRA: no activity
16		No	No	NMRA on advice of academic research/ethics committee. No regulations or guidelines; little experience in NMRA, no coordination of trials
20	○	No		Control by Ministry of Science & Technology, no Memorandum of Understanding, no regulations
26	○	No	**Yes**	Approx. 20 applications/year. Control through Council of Science and Technology (21 committees); NMRA grants approval and controls product importation. Guidelines not in line with WHO-GCP standards
SOUTH				
11	○●	**Yes**	No	200-300 applications per year. Approval by professional council; reporting of outcomes/adverse events to NMRA.
21	○	No	No	Responsibility of NMRA, but in practice controlled by a committee of which NMRA is a member. No ethics committee to supervise clinical trials.
MIDDLE				
05		---	---	**To be introduced** with new regulatory system
08	○○	No	**Yes**	Control by Health Research Division +Nat.Ethics Committee (not functional). Responsibility to grant approval not clearly defined. NMRA not involved at all
12		---	---	**No system**
17		No	No	**No activity** for ethical review or inspection, no GCP/GLP regulations or guidelines, no GMP or import control for investigational products
25	○	No	No	MoH regional committees, no central oversight. Draft regulations only. No import control or GMP for investigational products.
WEST				
01	○	No		No official structure, no regulations. Control by Res. Ethics Committee, of which NMRA is not a member. Lack of capacity to control clinical trials.
13	○	No	No	Need approval by MoH on advice of a research committee. Ethics committee exists but has no rules of functioning. **No control in practice**.
14		No		NMRA controls only studies conducted in connection with applications for MA. Outdated regulations
18	○○●	No	**Yes**	Ethical review by committee, approval by MoH, inspection by NMRA and ethics committee. No import control or GMP for investigational products.
19		Yes	No	Legal basis exists. No formally defined ethics committee
22	○	No	No	National Ethics Committee (not functional). No regulations, no regional committees; **no control in practice**
23	○	No	No	National research committee. No import control or GMP (incl. labeling) for investigational products. New draft regulations not to WHO-GCP standards
24		**Yes**	**Yes**	Guidance available for GCP; GMP mentioned but not required for licensing of investigational products

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1 Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States.

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3 Calculated as: Private expenditure on health as proportion of total expenditure on health × Out-of-Pocket expenditure as proportion of private expenditure on health

4 1933 legislation on the practice of pharmacy remains the basic legislative framework; NMRA was constituted by legislation of 1982.

5 A: Government Department , B: Board/Council/Body corporate, C: parastatal agency.

6 ** = Website introduced after visit [11] *** Website no longer found in 2009

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