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## Pharmaceutical Standards in Africa: The Road to Improvement and Their Role in Technological Capability Upgrading

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#### How to cite:

Banda, Geoffrey; Mugwagwa, Julius; Ndomondo-Sigonda, Margareth and Kale, Dinar (2015). Pharmaceutical Standards in Africa: The Road to Improvement and Their Role in Technological Capability Upgrading. In: Mackintosh, Maureen; Banda, Geoffrey; Wamae, Watu and Tibandebage, Paula eds. Making Medicines in Africa: The Political Economy of Industrializing for Local Health. Palgrave Macmillan, pp. 224–242.

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Version: Version of Record

Link(s) to article on publisher's website:

<http://www.palgrave.com/page/detail/making-medicines-in-africa-maureen-mackintosh/?isb=9781137546463>

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## 12

# Pharmaceutical Standards in Africa: The Road to Improvement and Their Role in Technological Capability Upgrading

*Geoffrey Banda, Julius Mugwagwa, Dinar Kale and  
Margareth Ndomondo-Sigonoda*

## Introduction

This chapter discusses standards, an elusive term and concept. For the African pharmaceutical sector especially, the term is used by the manufacturing sector, regulators, technical experts, procurement agencies, health system actors and policy makers to mean different things. There is a dearth of systematic studies that address what standards are, their classification and the logic behind their set-up and operation, and this has contributed to a huge asymmetry in understanding. The socio-economic, technical and political issues and how they have an impact on local production and industry development, including their effects on access to markets, have also not been systematically explored.

A common understanding of standards, their classifications and development, is important as the continent implements the African Union's Pharmaceutical Manufacturing Plan of Action (see also Chapter 15). Even more important is the need for African technical experts, regulators and policy makers to realize that standards and their development in the pharmaceutical sector is a process under their control. They can drive agenda setting and design realistic and context-sensitive road maps which align local industry development without compromising public health safety. The ability of policy makers to take a critical approach to the meaning and use of standards in the African pharmaceutical sector is an important enabler for designing road maps.

In this chapter we set up some of the issues that need further debate. We deconstruct standards and classify them into two groups; technically based standards and organizational or institutionally based standards. Technically based standards cover product, process, plant and environmental aspects. Organizational or institutionally based standards are those which are important for creating market confidence in firms' output through assuring the credibility and legitimacy of products, quality, production, distribution and recall processes. This credibility and legitimacy arises from physical inspections of production and distribution facilities, and the availability and examination of documentation and data management processes – administrative activities essential for endorsement, certification and accreditation.

We argue that this perspective helps to build an understanding of which types of standards are 'mutable'<sup>1</sup> – that is, judgement-based standards such as inspection, certification and accreditation for which capability building and improvement is a gradual process. By contrast, standards which cannot be compromised are those which deal directly with patient and public health safety concerns, namely quality, safety and efficacy of medicines. Such distinctions aid technical and policy people in designing and implementing appropriate interventions and road maps for technological capability and standards upgrading which do not compromise locally manufactured medicines' quality, safety and efficacy. These distinctions also help in crafting responsive, context-sensitive standards and compliance development processes that do not impose unnecessarily high costs or regulatory barriers on existing local industry. Our discussion of standards is informed by extensive literature searches, fieldwork in India, Kenya, Zimbabwe and South Africa where we interviewed technical experts in 2014, and interaction with regulatory and compliance experts in the UK.

## **A brief historical perspective**

The history of standards in the pharmaceutical industry is traceable to adverse events in patient safety, and one of the notable failures was the 1950–60s thalidomide disaster (Grabowski et al., 1978), in which a morning sickness pill containing thalidomide taken by pregnant mothers resulted in newborns with severe birth defects. The disaster catalysed stringent drug approval and monitoring processes, necessitating the passing of the Kefauver-Harris Drug Amendments Act in 1962 which called for proof of safety and efficacy in the approval process, approvals that now use animal testing and clinical trials that can take

up to 12 years. The logic for the development of stringent regulation was that there was a need for an independent government regulatory agency to ensure public health whose goals were not compromised by commercial interests of pharmaceutical companies (Abraham, 2002). All stages of the drug life cycle are regulated from drug discovery to release of the drug on the market (Harper et al., 2007). Table 12.1 summarizes five key stages in the life cycle of a pharmaceutical drug, and the regulatory requirements or standards pertinent for each stage.

For drug discovery, the key guideline is good laboratory practice (GLP), and for phase 1 to 3 clinical trials the guideline is good clinical practice (GCP). When the drug moves to the production phase, good manufacturing practice (GMP) becomes the guiding regulatory requirement, followed by good distribution practice guideline for distribution covering traceability of medicines (systematic identification of products) to aid in organized defective product recall from the market. For post-market surveillance, pharmacovigilance is the regulatory requirement. In addition, there is a wide range of other regulatory requirements at

*Table 12.1* Drug life cycle stages and regulatory requirements

Drug life cycle stage	Regulatory requirements/Guidelines
Drug discovery	Good laboratory practice (GLP): these guidelines focus on toxicological safety and protection of the test subject
Clinical trials (phases 1, 2, 3)	Good clinical practice (GCP): these guidelines consider product efficacy and safety evaluation, as well as individual protection and safety during testing
Manufacturing	Good manufacturing practice (GMP): these guidelines are concerned with assuring a manufactured product's quality, safety and efficacy, for both the product and the patient. The process aims to build in quality and ensure quality standards.
Distribution	Good distribution practice: these guidelines deal with storage, transportation and traceability for product recall.
Post-market surveillance	Pharmacovigilance: Sometimes called phase 4, this is monitoring of the product after market authorisation to check for any adverse events or product failure in all respects.

*Source:* Adapted from Harper et al. (2007) and Muller et al. (1996).

supranational and national levels, inspired by public health concerns and safeguards against drug disasters, to address trade and market entry obligations (Immel, 2001).

The situation is less complex and expensive for generic medicines, which are modelled on branded drugs, since proof of safety and efficacy has already been demonstrated for the branded drug. The generic drug producer needs at the minimum to demonstrate the equivalence of the drug for approval and it does not go through rigorous clinical trials. The bulk of medicines produced in Africa are generics, and consequently the standards that we will discuss in this chapter focus on generics manufacture. We do not cover standards in drug discovery and clinical trials.

While the first set of GMP guidelines for manufacturing, processing, packing or holding finished pharmaceuticals was introduced by the US Food and Drug Administration (FDA) in 1963 (Immel, 2000), the WHO has spearheaded the standards-setting process since the late 1960s, coming up with several amendments and extensions to the guidelines. In this chapter we focus on good manufacturing practice (GMP), defined by the WHO (2004) as the part of quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by market authorization. Many countries, including India, Kenya and South Africa, have developed their own GMP guidelines based on the WHO guidelines. The WHO is thus a global technical agency responsible for setting standards and normative guidance and for establishing best practice, all of which are implemented through national drug regulatory authorities (DRAs) and other relevant institutions. There is criticism, however, that the WHO sets standards for all its member states regardless of the level of development. There is also some questioning of the way in which the WHO has shifted from a solely advisory body (technical assistance included) towards acting as a regulatory body after it began pre-qualifications of pharmaceutical products for developing countries. WHO pre-qualification has acted as a catalyst for upgrading facilities in developing countries, but its stringent requirements have also been an impediment to market access to global donor-funded medicines purchase, in particularly for HIV/AIDS, TB and anti-malarial drugs.

## **Standards, their establishment and assurance**

A standard can be viewed broadly as a consensus between different agents to do certain key activities according to agreed-upon rules (Nickerson and Muehlen, 2006). This is a definition of standards as a process: a

common and agreed understanding of the rules of the game and how it is played, which resonates with the definition of institutions. These standards, therefore, operate on the back of strong institutional and organizational arrangements empowered to certify compliance with set rules through proclamations or a tightly controlled allocation of insignia or certification. Independent validation from a third party is critical for building confidence of other stakeholders who lack inside information or the means to gather credible information to make informed decisions. Standards therefore provide consumers with a basis for making informed consumption decisions and manufacturers with a benchmark of best practice (Nadvi, 1999) and hence a competitive tool.

A technology standard, on the other hand, is defined as 'a set of specifications to which all elements of products, processes, formats or procedures under its jurisdiction must conform' (Tassey, 2000: 58). This form of standards has been credited with the standardization that has significantly reduced manufacturing costs through economies of scale achieved by mass-production of similar or 'standard' components (Katz and Shapiro, 1985; Farrell and Saloner, 1986). It is argued that the presence of standards reduces uncertainty by providing actors with a framework that enables widespread diffusion of a technology (Rosenberg, 1976), as well as a modular approach to the production process where components can be manufactured by different producers.

Organizational or institutionally based standards interact with technology standards through the processes of data or process interrogation against set norms, validation, acceptance and certification. Thus certification and/or accreditation of products or firms affirm that accepted best practice (norms), 'standardized' and imbued with accountability, has been used at various stages in a product's design, development, manufacture, distribution and disposal. Specifically for the pharmaceutical sector, inspection, validation, certification, accreditation and regulation provide a system of traceability and accountability. This is done through detailed verification of quality-dependent procedures through internal and independent audits, quality training of personnel and constant monitoring of quality performance measures (Nadvi, 1999), as well as market performance and rectification in cases of failure.

Government departments, regulatory agencies, pharmaceutical companies' industry associations and other stakeholders play key roles in the design, implementation and refinement of policies and standards governing the sector. The credibility of a standard setting and monitoring process depends on the representativeness of the political process, how well it exploits existing technical knowledge, matches

context of application, and how committed participants are to the issue at hand (Fischhoff, 1984). These processes inherently reflect different interests, power structures and the resources of different stakeholders. Consequently and at the heart of this discussion, low-income countries tend to typically be 'standard takers' rather than 'standard makers', with the responsibility for implementation, monitoring and enforcement of the standards resting with the national governments (Stephenson, 1997), which in many African settings are resource-constrained. It is with this background to technical and organizational/institutional standards that we argue that African technical and policy organs need to gain a confident understanding that designing and implementing a road map to improving standards in the pharmaceutical value chain is something that is and should be under their control.

### **Standards as tools for competition and pressure to improve**

The significance of standards has grown over time and they have come to represent an important locus of collective strategy (Astley and Fombrun, 1983) within which the 'rules of the game' are set (Jain, 2012). For many producers and service providers in both the global North and South, compliance with international standards can add a competitive edge and form a necessary condition to access niche markets (Nadvi, 1999). More recent research emphasizes that standards provide opportunities and incentives for low-income countries to modernize local industry and strengthen supply of quality products (Jaffe and Henson, 2004; World Bank, 2005). This growing evidence base suggests that in low-income countries standards can link upgrading local industrial capabilities with supply of medicines and hence better local health service quality and inclusiveness (Nadvi and Waltring, 2002).

It has been argued that good-quality and affordable pharmaceutical products, whether imported or locally produced, depend largely on the outcome of standards-based competition (Narayanan and Chen, 2012). In the international trade literature, research suggests standards can be non-tariff barriers to trade (Stephenson, 1997; Wilson and Abiola, 2003), with regards to labour (Maskus et al., 2004; Maskus and Wilson, 2001) and environmental standards (Anderson, 1996; Anders and Caswell, 2009). These barriers emanate from inadequate provision of finance, local governance and regulatory structures. Kaplinsky et al. (2011) considered how standards such as hazard analysis critical control points (HACCP) and International Standards Organisation (ISO) are used as non-tariff barriers, especially for resource-constrained

countries. Supporting this assertion, a growing body of literature shows that without financial and technological support for domestic manufacturers, standards create significant cost and international market entry barriers (EC, 1997; Nadvi, 1999; Stephenson 1997).

International procurement practices and requirements of donors often enforce higher pharmaceutical quality standards than stipulated by national regulatory authorities. Implementation of these higher standards by local firms and achieving certification requires investment in people, equipment and changes in production organization as well as management practices – a costly exercise. Multiple accreditation caused by the need for local, regional and international certification such as WHO pre-qualification has direct negative bottom-line impact. One African firm reported during fieldwork that a WHO pre-qualification inspection can cost as much as US\$100,000, a large financial burden especially if accreditation and certification is not supported by success with global health and international medicine supply tenders. As a result, some local industrialists have questioned the logic of solving national-level institutional failure at supranational level. They argue that it is better to strengthen local regulatory authorities or take the harmonization route by solving the institutional challenges at national or regional level. These criticisms inform our critical discussion of standards, what they are and how road maps for improving standards and industry capabilities can be crafted.

## **The need to deconstruct standards**

A respondent from Kenya on being asked what standards were, remarked as follows: ‘this is where we have a problem...the word “standard” is misused both at global and national levels’. Such a remark underscores the need to deconstruct standards and classify them. He went on to describe what he considered to be standards, such as the guideline that describes good manufacturing practice (GMP) (which he termed a standard in itself), facility standards and personnel standards, as some of the key issues to be considered. In this section we discuss consecutively the two types of standards identified above: technical standards and institutional or organizational-based standards

### **Technical and process standards**

GMP guidelines are intended to be a set of minimum standards, covering recommendations on quality management, personnel, production facilities and equipment, documentation and records, production and



in-process controls, packaging and identification labelling, storage and distribution, laboratory controls, validation, complaints and recalls, and contract manufacturers (WHO, 2004). The diverse range of issues covered by GMP guidelines not only makes them a key and central lens for our discussion of pharmaceutical standards but also highlights why these guidelines are one of the most contested yet key drivers of the pharmaceutical industry. Under GMP we have chosen to focus on four standards that emerged as key in our research. Two of these standards (product and process) were classified as those which should not be compromised because of their direct relationship with patient and public health safety. The GMP process is critical for ensuring product quality, safety and efficacy. As noted in Chapter 3, GMP standards constitute a 'production culture' interwoven with professional judgement as regulators decide on what is deemed adequate especially for processes and facility standards.

#### *Product and process standards*

There was consensus among the multinational and local pharmaceutical manufacturers interviewed on the fact that product and process standards cannot be compromised. These they argued, should be the same wherever medicines are produced in the world. These standards are engineered in such a way that quality is built in and checked for at various stages and the evidence meticulously documented. The suppliers of raw materials have their facilities, processes and products vetted, and on receipt, raw materials are sampled and subjected to specific physical, chemical and biological tests. Raw materials are carefully stored ensuring avoidance of cross-contamination. There is a clear and documented chain of custody, traceability and accountability that is established along the whole process. In many African countries the production pharmacist is ultimately responsible and accountable for the release of batches of products after compliance with product and process standards as well as quality control tests. The quality control tests cover chemical, physical and biological characteristics of the product and avoiding contamination in the same three areas. Some of the tests, for example for tablets, include microbial tests, hardness and how well the tablet dissolves.

The drivers of product and quality standards are people, the production equipment and laboratory equipment. Improving standards therefore requires in many instances equipment and skills upgrading. For example, a Zimbabwean firm improved ingredient drying in the wet granulation tablet-making process by investing in a high-capacity fluid bed dryer. They also invested in automatic capsule-filling machines to improve standards and productivity. On the question of whether

technical standards change there were diverse opinions in the interviews. Some respondents argued that technical standards do not change, whereas some regulators reported that technical standards have become more stringent with time. One interesting perspective came from a technical expert who when asked by researchers in Tanzania whether very stringent GMP is necessary, argued that for infusions and injectables (parenterals), it was essential that they have to be sterile because they go straight into the bloodstream. However, he said, for tablets, the minimum safe requirements are different because they go into the stomach. Yet, he argued, current requirements are that they should be 'almost sterile', a standard hard to attain for manufacturers in Tanzania, and more stringent than essential good hygienic standards using good SOPs (standard operating procedures).

It is insights or perspectives such as these that need to be debated by those responsible for designing the road maps for upgrading standards in all their forms for the pharmaceutical sector. Our discussion, however, does not delve into the technicalities of GMP and the specific tests and indicators of quality. Our intention is to spark debate. In separate conversations, UK compliance experts acknowledge that there are different interpretations of GMP. What the US FDA means by GMP compliant is not necessarily what Europe's EMA means by GMP compliant and by extension what different African countries mean by GMP compliance. This argument resonates with the standards of the regulators as referred to by a Kenyan technical expert. It therefore becomes difficult according to the Kenyan expert to bring into one country a product produced in another, hence the African regulatory harmonization efforts described later in this chapter.

#### *Facility and personnel standards*

Another set of standards that technical experts in Kenya identified are facility and personnel standards. These encompass environmental and structural standards for buildings and health, educational and technical standards for personnel (which are often assumed). One Kenyan respondent remarked that '[facility standards] – that's where the problem of Africa lies'. He reported that facility standards are assumed but not clearly enunciated by regulators, and are especially problematic for old production facilities that have to be refurbished. A Kenyan respondent said, for example, that the WHO talks of 'competent people and suitable premises' in its requirements for pre-qualification – which, however, leaves a lot of room for different interpretations. Facility standards are linked to environmental standards and determine air quality and

freedom from contamination through physical separation. Personnel standards include technical know-how, hygiene standards (medical check-ups included) and administrative skills as discussed later. Thus personnel standards cover diverse skills sets depending on functions, which might include but are not limited to analytical and organic chemistry, microbiology, plant engineering, production, pharmacovigilance, quality assurance and research and development. Facility and personnel standards formed the class of standards for which improvement, according to the technical experts we interviewed, should be approached in a gradual and cumulative manner. In Tanzania, regulators reported that they know that the firms are growing and they give them 'timelines' for improvement. These are the classes of standards that we classify as being mutable.

### **Organizational/institutional aspects of standards**

The supply of medicines and other medical products into the health delivery systems is intensively regulated and governed by strict product, process, marketing and institutional standards. The need for regulation comes from information asymmetry between the producers on one side and patients and clinicians on the other side. Patients cannot assess safety or observe quality and efficacy of medicines on their own, and neither can the medical practitioners who decide on their behalf (Harper, 2007). This is where regulatory bodies come in, by seeking evidence of compliance with guidelines, rules and regulations to give credibility and legitimacy to organizations inspected. Accreditation and certification are an institutionally based regime of standards that are built on and meant to validate the technical, process, facility and personnel standards as reflected in the various guidelines such as GLP, GCP, GMP, Good Distribution Practice and pharmacovigilance.

The challenge for Africa rests in skills shortages at the regulator and among compliance managers at firms. As the firm operates, it records data which must be managed and produced as evidence to the regulators (inspectors). This process requires someone with a technical background who also is conversant with data management and documentation. The regulators in addition to the physical inspections also analyse documents and check against the set norms. As discussed earlier, this is where the judgement of the assessor (regulator) comes into play. These standards are of an organizational and institutional nature and are dominated by soft issues of training and retaining human capital.

These institutional/organizational standards tend to be resource-driven and path dependent. Their evolution depends in part on historical

legacies of national institutions, industrial capabilities and tertiary training that included practice-based polytechnic training. South Africa and Zimbabwe as a result have relatively well-developed medicines regulatory systems. For South Africa the main piece of legislation shaping pharmaceutical standards is the Medicines and Related Substances Control Act (1965) and its various amendments. The Medicines Control Council (MCC), a public sector body tasked with regulating pharmaceutical products in South Africa has eleven expert committees, which evaluate the safety and efficacy of a drug submitted for approval and they inform the decisions of the MCC. Apart from the Registrar of Medicines, all members of the MCC committees are engaged on a part-time basis, including the evaluators, who are often in full-time employment elsewhere. There is, however, concern on such a heavy reliance on external expertise.

The Medicines Control Council (MCC) comprises four units, inspectorate and law enforcement, operations and administration, clinical and medicines registration. These units perform an administrative and coordinating role, facilitating the work of the expert committees. The MCC works within, and is influenced by, the public sector institutional context, as well as serving as the local competent authority for monitoring implementation of requirements from agencies such as the WHO, FDA and ICH in pharmaceutical manufacturers operating in South Africa. In terms of skills, respondents in South Africa also identified loss of regulatory skills especially at regulatory bodies as a key challenge. They reported that it took a long time to train a competent regulatory person, especially those with industrial experience, and as a result they are perpetually in training mode. The firms also reported that they face the same skills training and retention problems.

#### *Harmonization to upgrade regulatory standards*

An interesting issue identified by experts in the Kenyan pharmaceutical industry was the issue of the 'standard' of the regulatory bodies themselves. Different countries have different regulatory capacities and capabilities. Highly resource-limited countries do not have the same capacity and capabilities as resource-rich countries. As a result, manufacturers fear that accreditation by one country does not equate to the same level of stringency as accreditation by another. Interviewees reported that some countries in the East African region had few regulatory pharmacists who looked at dossiers and at the same time had to do factory inspections – an impossible task.

These realities are some of the catalysts for regional medicines harmonization initiatives such as the African Medicines Regulatory

Harmonisation (AMRH) initiative led by the New Partnership for Africa's Development (NEPAD). In recognition of regulatory capacity limitations for some countries and its consequent socio-economic impact, NEPAD Agency undertook, in collaboration with partners<sup>2</sup> to initiate the African Medicines Regulatory Harmonization (AMRH) Programme since 2009. The AMRH initiative is part and parcel of the implementation of the African Union Pharmaceutical Manufacturing Plan for Africa (PMPA) (see Chapter 15) and aims to facilitate access to quality, safe and efficacious medicines to the African people by working through the existing political structures, and the regional economic communities (RECs).

In particular, the initiative aims to catalyse the establishment of effective national, regional and continental medicines regulatory agencies, and has made significant progress since 2009 in Eastern, Western and Southern Africa towards transparent, efficient and effective regulatory systems that provide assurance of faster approval of medical products and technologies that meet internationally acceptable standards of quality, safety and efficacy. Some of the key aspects focussed on are harmonized guidelines for registration of medicines, good manufacturing practice (GMP) inspection guidelines, quality management systems (QMS) and information management system (IMS).

Through NEPAD Agency's coordination, the East African Community (EAC) successfully launched the Medicines Regulatory Harmonization (MRH) programme in March 2012, and is now at implementation stage with substantial progress made in the endorsement of the harmonized guidelines for registration of medicines, good manufacturing practice (GMP) inspection guidelines, quality management systems (QMS) and information management systems (IMS). The NEPAD Agency has undertaken to expand the AMRH programme to other RECs beginning with the Economic Community of West African States (ECOWAS) through its health agency, the West African Health Agency (WAHO) in collaboration with the West African Economic and Monetary Union (UEMOA). The MRH Programme for West Africa was launched on 2 February 2015. Progress has also been made on implementation of the programme in the Southern African Development Community and central African regions.

#### *Cost implications of standards*

Regulation raises numerous questions concerning compliance costs in relation to benefits obtained, transaction costs associated with regulatory administration and enforcement, and unanticipated or unwanted responses on the part of the regulated industry. Regulations may have

high individual compliance costs, which are compounded by the fact that organizations are simultaneously attempting to comply with other, possibly conflicting regulations. When regulatory standards or mechanisms conflict, they may prevent one another from achieving their intended benefit. Increasing legislative controls in highly complex, and heavily regulated arenas such as health care can lead to ‘regulatory inflation’ rather than enhanced compliance. Moreover, the risks of compliance failures and regulatory inflation are heightened in the field of healthcare because jurisdiction is often fragmented and operates at multiple layers from global to local levels (Mugwagwa et al., 2015).

The consensus from South African respondents with respect to standards was that innovation, technological capability upgrading and health delivery were cost-sensitive processes, and that while adopting and keeping standards came at a cost, higher costs were being incurred from policy and regulatory uncertainties on the one hand and inefficient quality assurance systems on the other. Trying to curb costs today by compromising on standards would lead to ‘fewer drugs to treat current and future generations’, but taming the policy and regulatory jungle to ensure cost-effective and sustainable compliance with standards would be good for companies, regulators and patients in the short and long runs. Multiple accreditation has direct bottom-line impact.

### **The Kenyan standards and upgrading road map**

Respondents in Kenya were in general agreement that product and process standards are necessary and that they should be seen as ‘minimum regulatory expectations’ required to manufacture a product that meets specific needs, that is, fits the purpose for which it is made. Kenya has developed a road map for upgrading standards. They acknowledge that it is a gradual process requiring multi-sectoral coordination and concerted efforts. In an interview, an industry expert involved in designing and developing the road map for the country said:

So we came up and said you must solve the problem, but it’s not a small one... we looked at the whole scenario and came up with seven key areas

which are detailed below as direct quotes:

1. You must have a road map for the local industry to improve because you cannot shut down any one of them because they have been producing.

2. You must have a system where you check the quality of the product on the market and remove the ones which are not performing and remain with those which are performing well.
3. You must have someone overseeing the market and industry and that is the regulator, you must incentivize the capacity and improve its capacity.
4. Whereas the industry is trying to achieve the standards, it's going to cost money, so you should look for a way where they can get the money.
5. You must provide the incentives for the time the industry is improving, they must not improve and lose their market, so you must protect it and come up with incentives that will help them.
6. You must come up with a strategy for capacity building of human [skills], their capacity to undertake this both in the regulatory and in the private sector
7. There are those items which are essential for the industry to place their products on the market, but not one single company can do it alone, so you must put them together and see how they can be shared, and this is what you call the support services or shared platform.

Recognizing that they could not do all seven activities at once, they prioritized the first initiative. They developed the road map, and by mid-2014 the technical aspect had been completed and they were waiting for the narrative part of the document, endorsements and final launch. A concerted effort to involve industry, regulators and the Ministry of Industrialization was made during the process of developing the road map (Technical Expert, Kenya, 2014). The technical expert through his networks brought together the ministers for health and industrialization in a joint meeting to discuss the road map.

### **Money for upgrading processes and standards**

Kenya realized that the process of upgrading production facilities and machinery would impose financing constraints on affected firms. The fourth point in the strategy above deals with the need to facilitate funds availability. To that end they engaged the Kenyan Bankers Association, who informed them of their fears about funding pharmaceuticals production. According to the pharmaceutical industry respondent, the bankers said: 'We are risk-based institutions, we go only where there is less risk, but in pharmaceuticals the risks are so high that we dare not'. This statement points to issues of finance capability on the part of banks (see Chapter 15). Reinforcing the challenge of finance capability,

one respondent cited an example of a Development Bank which refused to fund a quality control laboratory because they said they could not demonstrate what would come out of the laboratory. The pharmaceutical technical expert argued that the bank failed to see the overall picture and how the quality control laboratory would result in better production processes and products. The bankers themselves acknowledged that they lack a deep appreciation of the industry dynamics:

We have never got an expert who we can trust to go there [pharmaceutical industry] and do an evaluation; and I said to them then I should become a banker. (Technical expert, Kenyan pharmaceutical sector, 2014)

Efforts are under way to bring industrialists and bankers together to try and bridge the gap in knowledge about the sector and hence improve risk analysis. Kenya's road map, however, evidences a purposive and integrated approach to improving standards and upgrading facilities. In interviews the technical experts acknowledged that this would be a long process the success of which depends on availability of resources for investment in equipment and people. The programme in Kenya is being supported by UNIDO, supplementing limited national resources allocated to this important initiative. Kenya appears to be taking control of the issue of standards, and although they are still at the initial steps of implementing the programme, there are lessons that other African technical and policy people can learn.

Initiatives focusing on building capacity and capabilities on standards in local manufactures require coherence/harmony between different approaches. Some global institutions working with African countries, such as the WHO, take a product-by-product approach to standards (WHO pre-qualification), whereas UNIDO and GIZ take a systemic technological approach. This helps to explain different approaches to improving standards in African countries. UNIDO and GIZ prefer to build local technical skills by training local industry. In the next section we look at the Indian standards upgrading to extract lessons that Africa can use.

### **What lessons can Africa learn from the Indian GMP upgrading road map?**

Over the last three decades the Indian pharmaceutical industry has emerged as a major supplier of cheap generic drugs across the world.



The Indian government was credited for infusing life into the Indian pharmaceutical industry through industrial and regulatory policy intervention, and the success of the Indian firms made these interventions a recipe for pharmaceutical industrial development in other emerging countries (see also Chapter 10).

Pharmaceutical production in India is governed by the Drugs and Cosmetic Act of 1940 and the much amended Drug and Cosmetics Rules of 1945. The Act and Rules regulate drugs imported, manufactured, distributed and sold. No pharmaceutical products can be imported, manufactured, stocked, distributed or sold unless they meet the quality standards laid down in the Act. An Indian Pharmacopoeia was published in 1955, and over the years problems in controlling spurious or counterfeit medicines have dominated Indian policy agendas. The Indian government initially aimed to enforce GMP standards in all pharmaceutical manufacturing firms via the Drug Policy of 1986. This laid down requirements for GMP adherence in Schedule M of the Rules, which came into force in 1987. Schedule M was strengthened to require WHO-GMP standards, by amendment in 2001, with the aims of ensuring that firms upgraded and of eradicating counterfeit and substandard drugs. Those pharmaceutical firms that did not comply with these regulations have been refused manufacturing licenses from each State Drug Control Administration office. In the case of manufacturing plants approved before December 2001, non-compliance led to their licenses being revoked, forcing closure of these manufacturing facilities.

The financial cost involved in complying with GMP has proved a significant barrier for small companies in India to upgrade manufacturing facilities. Upgrading of manufacturing plants by small scale firms would result in those firms graduating to become medium-scale firms, thereby losing the tax benefits and other concessions available to small scale enterprises. The Indian government responded to this issue by providing some concessions for the Indian firms, increasing investment limits and turnover thresholds for eligibility as a small-scale firm. On the other hand, several large-scale companies upgraded their plants to access high-income country markets, and their significant financial resources made this transition feasible. The deadline for implementation of GMP was postponed from 31 December 2003 to 31 December 2004, and then postponed again until 30 June 2005. Each State Drug Control Administration office also had the authority to extend the deadline of compliance within its area of jurisdiction.

In spite of these concessions, this mandatory application of GMP had a significant impact on the Indian pharmaceutical firms. According to

official estimates, in 2001, 327 pharmaceutical manufacturing plants closed, had their licenses suspended, or were forced to shift to some other state. A total of 370 plants were not in a position to comply with GMP and have closed since 2005 (Planning Commission, 2002, par. 7.1.192). In addition to an increase in competitive pressure, GMP compliance has been another force that has induced the exit of small firms from the market. However, the introduction of GMP has also contributed to the enhancement of trust in Indian products in the global market. In addition, complying with GMP standards of the US and Europe has increased exports to Western countries and expanded the opportunity for contract manufacturing.

Since 2000, the strong presence of the Indian firms in the markets of advanced countries, and specifically in the US, has brought severe scrutiny from regulatory agencies around the world. More numerous FDA inspections led to an increase in the number of warning letters and import bans for the Indian firms (see also Chapter 6). The FDA has identified a number of Indian pharmaceutical manufacturers who have had problems with data integrity and GMP at their respective facilities. Gaffney (2015) notes that since GMP data are intended to ensure that products meet pre-established specifications, absence of credible data management creates concern that these products cannot be trusted.

The case of Ranbaxy provides a prime example of the FDA attitude towards implementation of GMP in the Indian firms. The FDA has repeatedly issued warning letters and import bans to two of the company's manufacturing plants because of data integrity issues. The warning letters note that the FDA has concerns about non-compliance with US current Good Manufacturing Practices requirements, although 'FDA has no evidence of harm to any patients who have taken drugs made in these two facilities' (Jeffrey et al., 2001; US Food and Drug Administration, 2008). Elaborating on their concerns at one of the manufacturing plants, the FDA warning letter focuses on concern that 'written records of major equipment cleaning and use are inaccurate' (USFDA, 2008) and notes that their investigative team uncovered 14 instances 'where... records for equipment used in manufacturing operations... included initials or signatures of employees who reportedly verified cleaning of equipment but were not shown as present by security log records' (USFDA, 2008).

Jeffrey (2001) argues that this experience highlights the way in which international regulatory authorities play a crucial and detailed role in setting production and data management standards at the Indian manufacturing sites, using the set of regulations and rules developed to

protect high-income countries' consumers. The cost of implementing and complying with these regulations is incurred by the Indian manufacturers and government and in most cases passed on to the Indian consumers. Further, these regulatory troubles have caused the Indian firms significant revenue losses and reduced competition in generic markets, contributing to profit margins of multinational pharmaceutical companies. This experience raises issues about the authority of developing country governments in setting standards, and about the appropriateness of international standards to the local context in the developing countries.

## **Concluding discussion**

Pharmaceutical standards and regulations are necessary yet complex institutions which change over time, operate at various vertical and horizontal scales, are subject to different interpretations and applications and have potential to assist the manufacturing of, and access to, safe efficacious medicines. However, they can also act as undesirable market entry barriers. African pharmaceutical industry players accept that standards are important, but they contend that the other regions of the world which are more advanced now 'did not themselves improve their standards overnight'. Rather, it was a gradual and long drawn-out process as countries learned best practice from the first movers. African technical experts argue that Africa should not be pressured to catch up 'overnight'. When African and other developing countries look broadly at pharmaceutical standards, they need to view them as a process, and there is therefore a need to introduce clear road maps for a gradual strengthening of the requirements for standards, driven by local or regional regulatory institutions.

We conclude that in order to improve standards and upgrade technological capabilities, first, standards need to be deconstructed and understood based on risk management principles. Second, institutional or organizational standards that are based on judgement and can be gradually improved should be recognized as mutable in that sense. Third, technically based standards should also be viewed from a risk management perspective. Once this has been done, African technical and policy actors need to take control of the issue of pharmaceutical standards and to design and manage context-sensitive regulatory frameworks and road maps backed by an evidence base that draws from a clear understanding of standards, attendant risk profiles and their role in industry development and access to medicines.

## Notes

1. We acknowledge Dr Farah Huzair for proposing the terms ‘mutable and immutable’ standards at an Innogen Knowledge Exchange workshop on African Local Pharmaceutical and Medicines Supply held in London in 2013
2. The African Union Commission (AUC), Pan African Parliament (PAP), the World Health Organization (WHO), the World Bank (WB), the Bill and Melinda Gates Foundation (BMGF), the UK Department for International Development (DFID), the Clinton Health Access Initiative (CHAI) and the Joint United Nations Programme on HIV/AIDS (UNAIDS)



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