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# Standards and Their Role in Pharmaceutical Upgrading in Low- and Middle-Income Countries

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The supply of medicines and other medical products into health delivery systems is intensively regulated and governed by strict product, process, marketing and institutional standards. The regulations and standards cover the lab to bench value chain; research and development, proof of concept, proof of efficacy, followed by authorisation and registration for production, marketing to the public and post production/marketing surveillance, monitoring and recall. It has been argued that the history of standards in pharmaceutical products is traceable to adverse events in patient safety. Notable failures of patient safety were amply demonstrated by the 1950/60s thalidomide disaster, where a morning sickness pill containing thalidomide taken by pregnant mothers resulted in new-borns with severe birth defects. This disaster catalysed stringent drug approval and monitoring processes. This necessitated the passing of the Kefauver-Harris Drug Amendments Act in 1962 which called for proof of safety and efficacy in the approval process that now uses animal testing and clinical trials and can take up to 12 years. This process is followed for new drugs that need to be launched onto the market. The situation is slightly less complex for generic medicines modelled on expired branded drugs, as proof of safety and efficacy would have already been demonstrated. The generic drug producer needs at the minimum to demonstrate the equivalence of the drug for approval, and as such, does not go through rigorous clinical trials taking up to 12 years. The bulk of medicines produced in developing countries to cater to health requirements are mostly generics, which do not have high margins like the branded drugs produced through the blockbuster model.

Government departments, regulatory agencies and industry associations play a key role in the issue of standards. They have instituted procedures and laws that assure quality in Chemistry, Manufacturing and Controls (CMC) for pharmaceuticals, addressing conditions that may be harmful to patient health. There are numerous contentions, however, about the impact of standards on pharmaceutical sector development in particular, and health delivery in general in developing countries. These contentions range from who sets the standards and in whose interests to whether or not enough is being done to purse alternative, easier-to-sustain but equally effective standards for developing countries given their manufacturing capabilities and health system requirements.

## PURPOSE

This policy brief draws on a pilot study carried out in 2014 in India, Kenya and South Africa by Innogen Institute researchers with funding from the Open University's Innovation, Knowledge and Development (IKD) Research Centre, to engage with some of the issues above, with the objective of contributing to clearer understandings on *'what standards are, which standards are mutable and which ones are immutable and whether standards are hindering or promoting innovation, technological capability upgrading and the making of medicines in low and middle income countries'*. The pilot study encompassed extensive literature reviews and interviews with up to 30 respondents representing pharmaceutical and biotech industry experts, academia, science policy think tanks and innovation consultants, industry associations, regulators and related others in the study countries.

Our main finding and the key message of this policy brief is that while standards for the pharmaceutical industry are sometimes seen as independent drivers of technological capability upgrading, the reality is far more complex. Standards in pharmaceuticals change over time and are shaped by a complex mix of firms' innovations, lobbying, procurement politics and market protection. Consequently, standards may both help to ensure safe and efficacious medicines, and also act as an undesirable market entry barrier.

This policy brief and the broader work underpinning it seek not only to draw attention to standards and their effects on health innovation and technological capability upgrading

for sustainable pharmaceutical manufacturing in developing countries, but will hopefully contribute to better health delivery and access to medicines options in developing countries.

## CONCEPTUAL AND ANALYTICAL FRAMEWORK

Fully aware that standards are an integral part of innovation systems, we draw on the national innovation systems perspective and thematic analysis for our conceptual and analytical framework. We define innovation broadly as the creation and use of new, better, more effective and more acceptable products, technologies, processes and ideas (Mulgan and Albury 2003[1]). We are also in agreement with the neo-Schumpetarian thinking (see for example Pyka et al, 2009[2]), which argues that systems of innovation do not emerge from industrialisation or technological advancement efforts only, but as Edquist (1997[3]) notes, from processes that are 'lengthy, interactive and social; [and in which] many people with different talents, skills and resources have to come together'. Innovation systems require deliberate development and embedding within country-specific institutional and technological contexts (Lundvall, 1985[4]).

## ANALYSIS AND DISCUSSION

Our empirical data from the three study countries and literature searches generated the following insights:

### The problem lies elsewhere?

Indeed the role of standards is not only complex, but is also often misunderstood and misinterpreted, leading to contested views on the impact of standards on innovation and technological capability upgrading specifically, and access to medicines broadly. Part of the complexity and ambiguity arises from the contested use of the term *standards* and subsequent practice 'mix-up' of terminology and meanings amongst *standards*, *regulations* and *procedures*; which are often used interchangeably and assumed to carry the same meaning and focus. There are key differences amongst *standards* (specific voluntary or mandatory controls that help enforce policy), *procedures* (step-by-step instructions for implementing standards) and *regulations* (legislation, whose use is mandatory). These differences have policy and practice implications for development of local production capabilities.

Manufacturing, process, quality, packaging and product standards were agreed by our respondents to be an integral part of the pharma industry, and that they do not need to be changed, as this would pose immense safety, credibility and reputational risks. As one respondent noted, instead:

*"What needs to be focused on are the regulations, procedures and other measures that are aimed at building, optimising and sustaining standards within manufacturing systems. Instead of generating or focusing on the negative side of standards, pharmaceutical companies in developing countries should focus on developing quality assurance systems which are capable of sustaining existing standards and taking on board new standards".* **Respondent X1, South Africa**

By ensuring that products are 'fit for purpose' and that the manufacturing process gets products 'right first time', the role of standards in cost-cutting is often understated. One of the biggest challenges for the local pharmaceutical industry in the three study countries are the different and often fluctuating sets of regulations, such as price and profit margin controls, and marketing and advertising requirements for the low-margin generics production business model, which adversely affect pharmaceutical revenues and long term sustainability. These regulations are downstream of the manufacturing process, unlike the technical manufacturing and product standards, hence their impact is more difficult to predict or control. Price controls in particular were said to lead to less competition in the market for generics as most companies saw business as unviable. They were also said to be delaying new product launches by serving as a dis-incentive for R&D and innovation. Policy uncertainty (including incoherence) was also said to be one of the more notable hindrances to innovation as companies would often resort to costly measures and strategies unmatched by resultant profits to navigate the policy terrain.

In summary, there seems to be some consensus from the South African respondents that innovation, technological capability upgrading and health delivery were cost-sensitive processes. Additionally, 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 run.

### Need to unpack standards

Similar to South Africa, respondents in Kenya were in general agreement that standards are necessary and that they should be seen as 'minimum regulatory expectations' required to manufacture a product that meets specific needs, i.e. fits the purpose for which it is made. Standards exist for varied aspects of the pharmaceutical sector including quality, safety and efficacy covering processes, premises, machinery,

[1] Mulgan, G, Albury D: Innovation in the public sector. Strategy Unit; Cabinet Office; United Kingdon; 2003.

[2] Pyka A, Cantner U, Greiner A, Kuhn T (2009): Recent advances in neo-Schumpetarian economics: essays in honour of Horst Hanusch. Edgar Elgar Publishing; USA and UK; 2009.

[3] Edquist C: Systems of innovation. Technologies, institutions and organisations. Pinter; London and Washington; 1997.

[4] Lundvall, BA: National systems of innovation. Towards a theory of innovation and interactive learning. Pinter; London; 1992.

the environment, materials, people and stock rotation, amongst others. Standards also traverse different levels from the global to the local. With respect to manufacturing, some examples of key process standards identified were: good clinical practice (GCP), good manufacturing practice (GMP), good laboratory practice (GLP), international common technical documents (ICTD) and pharmacovigilance standards that have risen to prominence in the last 10 years or so. Facility standards are to a large extent often forgotten; encompassing environmental and structural standards for buildings and health, educational and technical standards for personnel (which are often assumed). For example, the WHO talks of "competent people and suitable premises" in its requirements for pre-qualification, and which leave a lot of room for different interpretations.

There is a need for coherence/ harmony between different approaches to standards. Some global institutions, for example the WHO, take a product approach to standards (WHO-prequalification), whereas UNIDO and GIZ take a systemic approach. This explains the different approaches to improving standards in African countries. UNIDO and GIZ prefer a systemic approach of building local capabilities and capacities by training and offering technical assistance to local industry on upgrading production facilities and up-skilling the pharmaceutical sector players. These different approaches have both economic and regulatory impact on the pharmaceutical sector. Indian industry associations and manufacturers are in favour of harmonisation of standards. They also pointed out incoherence in the regulatory structures that devise and implement standards.

## The politics of standards

On the other hand, while standards were viewed as good, respondents felt that in terms of markets for pharmaceutical products, standards were often used as a convenient and suave trade and politically correct technical tool for barriers to entry for developing country manufacturers, especially in their quest to win international tenders for medicines and other medical products. An industry respondent from India noted that while on one side standards have emerged as an integral part of quality healthcare, 'on another hand they are also viewed as a tool used to maintain prevalent global monopolies'. With respect to tendering processes for example, one respondent mentioned that some donor countries had overplayed the standards card and there was pushback from East African countries, particularly on the insistence of WHO-prequalification on tenders. A quality assurance expert argued:

*"... that WHO-prequalification was not a standard but a "club membership" because if you do not meet the set criteria there was no punitive action taken but you would be "kicked" out of the club"* **Respondent X2, Kenya**.

African pharmaceutical industry players accept that standards are important, but they contend that the other regions of the world that are advanced now 'did not themselves improve their standards overnight', but it was a gradual and long drawn-out process. They argue that Africa should not be pressured to catch up 'overnight'. When Africa, and developing countries broadly, look at pharmaceutical standards, they need to view them as a process and there is, therefore, a need to introduce clear roadmaps that show a gradual strengthening of the requirements for standards driven by local or regional regulatory institutions.

## CONCLUSION

Based on documentary analyses of global, regional and national pharmaceutical sectors and buttressed by data from interviews with key actors in the area of pharmaceutical standards and regulation in selected developing countries, this policy brief shows that the contention, and indeed the evidence, is that 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;
- Have much potential both to help manufacturing of and access to safe efficacious medicines; and
- Act as an undesirable market entry barrier.

We conclude that in order to develop and sustain local pharmaceutical production capabilities, developing countries will have to manage a delicate balance of devising agile regulatory frameworks backed by a clear understanding of standards and their role in crafting appropriate technical, social, economic and policy conditions, which will not compromise provision of high quality, efficacious and affordable healthcare products to local populations.

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