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The quality of medicines

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The quality of medicines: an ethical issue?

RAFFAELLA RAVINETTO, BENEDETTA SCHIAVETTI

Introduction

The Hippocratic maxim, “Do no harm,” is a long-standing fundamental principle of medical ethics, encompassing both medical practice and medical research. Yet, not enough attention is given to the implications of this principle for sectors related to medical research and practice, such as the pharmaceutical sector. The regulation of the standards of quality in pharmaceutical production and distribution, for instance, is generally considered a purely technical – rather than ethical – subject. Poor enforcement of regulatory supervision of manufacturers and wholesalers of medicine exposes the end-users to low-quality pharmaceutical products, which will result in avoidable “harm,” such as therapeutic failure, emergence of resistance and even direct toxicity. A glaring example of this in recent times was the death, in Pakistan, of 120 cardiovascular patients who had received a medicine contaminated with pyrimethamine (1). Due to the globalisation of the pharmaceutical supply chain and the lack of international regulatory oversight, stringent drug regulatory authorities in affluent countries are also exposed to challenges related to quality. In the USA, for instance, at least four patients died after using contaminated heparin from China (2). These and other unnecessary deaths, caused by medical products which harmed rather than benefited the patients, are unacceptable and should be questioned on ethical grounds.

The Indian pharmaceutical industry plays a unique role at the global level. In addition to supplying the national pharmaceutical market, it is a major exporter of drugs to both affluent and low- and middle-income countries (LMICs). On the one hand, India supplies about 40% of the generic and over-the-counter drugs consumed in the USA. On the other, it is widely referred to as the “pharmacy of the developing world” because of the essential role played by Indian

manufacturers as global suppliers of affordable essential medicines, in particular, products used for the treatment of some of the most burdensome diseases in poor countries (eg HIV, malaria and tuberculosis). However, in recent years, there has been increasing controversy about the weaknesses in pharmaceutical regulation and consequently, the variable standards of the quality of Indian medicines. The current debates may be broadly classified into three threads: those based on documents and reports coming from India itself; those concerning the quality of Indian medicines exported to high-income countries (HICs); and those concerning the quality of medicines distributed in LMICs.

Reports from India

In 2012, a report of the Indian Parliamentary Standing Committee on Health and Family Welfare documented the shortcomings of India’s drug regulatory authority, the Indian Central Drugs Standard Control Organisation (CDSCO). These included understaffing, a dearth of medically qualified staff, collusion with the pharmaceutical industry, weak infrastructure and poor interdepartmental coordination (3). According to the report, the CDSCO lacks the resources and capacity to ensure the effectiveness, safety and quality of the medicines manufactured in India, to be distributed within the country or exported abroad. The content and recommendations of the report had vast ramifications, both in the national and international contexts (4,5), and many advocated for strengthening of the CDSCO and a reorientation of its activities towards a patient-centred approach. The publication of the report of the Standing Committee undoubtedly created a momentum that could have led to radical reform of the Indian regulatory authority. Unfortunately, such a process has not been started yet, or even if it has, it is not receiving due attention from the national and especially from the international press.

Reports from high-income countries

After the publication of the report of the Standing Committee, the decisions of some strict drug regulatory authorities in HICs concerning medicines imported from India have prompted further doubts about the quality of Indian pharmaceutical products. For instance, the US Food and Drug Administration

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(US FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued recalls for two products that did not conform with some of the required specifications (the failure to pass the dissolution test, which is an indicator of a product's bioavailability, and the possible presence of impurities above permitted limits, respectively) (6). Health Canada banned imports from three Indian facilities because of problems with data collection and doubts about the quality and safety of some of the products and active ingredients used at the manufacturing sites (7).

These reports surely point to real problems, which need to be corrected. However, their significance may have been misunderstood. First, even if the spotlight of the international press has been on the quality of medicines imported into the USA, the UK and Canada from India, the failure to pass regulatory inspections or prove the efficacy and safety of a given product or batch of a product is certainly not limited to Indian manufacturers. This can be easily verified in the US FDA website, where the agency's warning letters are made available to the public (<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/>). Specific cases of Indian manufacturers failing to meet the requisite standards might have been highlighted more than others because of the important role played by India as a supplier of medicines for HICs, especially in the last decade.

Second, those Indian companies that export to strictly regulated markets agree to comply with the quality standards set by the recipient country and to be regularly evaluated by the stringent drug regulatory authorities there. The detection of quality-related problems in a manufacturing site, the notification from the regulatory body to the company, and the corrective actions that the company is bound to carry out, are, *per se*, the sign of a stringent quality assurance environment. To classify those companies that fail to successfully pass a regulatory inspection as bad companies *tout court* would be an oversimplification. Such transparent regulatory mechanisms allow us to be aware of the weaknesses of these companies, while we may remain unaware of the weaknesses of other Indian and non-Indian companies that do not export to strictly regulated markets, and do not undergo such stringent regulatory supervision.

Reports from LMICs

A working paper issued in 2014 by the US National Bureau of Economic Research (NBER) raised new doubts and questions about the quality of generic medicines manufactured in India and exported to Africa (8). The researchers analysed 1470 samples of antibiotics and medicines for tuberculosis, labeled "made in India" and purchased in five cities in India as well as in 17 African and non-African LMICs. Reportedly, they found that a significantly higher proportion of the poor-quality products were purchased in Africa, and concluded that Indian companies generally adopt lower standards for medicines sold in Africa. However, the exclusive focus on products labeled "made in India" prevents any comparison with the supply of poor-quality medicines originating (or

having been declared to have originated) in other countries and available in the same markets. It should also be noted that the labeling requirements for medicinal products are not harmonised among the African countries, so establishing the origin of a medicine with certitude is not easy. The authors of the report acknowledge this: "Being labeled 'made in India' does not necessarily mean the actual manufacturer is an Indian firm. In a few instances we obtained information that samples were faked by organised criminals from China." The failure to comply with product specifications, eg poor storage conditions along the supply chain, might also lead to degradation of the product. Furthermore, the quality of the medicines was tested not through full quality control laboratory testing, but with the GPHF-Minilab® (Global Pharma Health Fund), a portable technology for semi-quantitative evaluation of the drug content, which has low specificity and sensitivity (9). A structured survey carried out by the World Health Organisation (WHO) in different African countries showed that the frequency of quality defects identified by GPHF-Minilab® in surveyed anti-malarials was different than that determined with laboratory testing, and that it cannot be concluded that this technology ensures the identification of all poor-quality medicines (10). There is surely a need to increase the knowledge of the proportion, distribution and types of medicines of poor quality to enhance the focus of political and regulatory actions (11). The survey undertaken by the NBER has made a contribution in this respect, but when comparing data from reports and the scientific literature, the collection of data should follow the existing proposed guidelines, such as the Medicine Quality Assessment Reporting Guideline (12) and the soon-to-be-published WHO "Recommendations on the content of a survey protocol for surveys of the quality of medicines" (13).

It must be noted that the original NBER report was not published in an international peer-reviewed journal. However, it received a great deal of publicity in the international medical press (14,15), leading to a general perception that it was published in such a journal.

The way forward

In a paper published in 2013 in this journal (5), it was suggested that "the variable regulation of medicine quality in India has both direct and indirect negative consequences for public health. On the one hand, it may allow poor-quality medicines to reach patients, causing unnecessary morbidity and mortality, mainly among the most vulnerable populations in India and elsewhere; on the other hand, it delegitimises its own quality products, which are fundamental to expand health coverage at both the national and global levels". Two years later, nothing seems to have changed substantially. Despite reports that significant work is in progress to correct the weaknesses pointed out in the CDSCO by the Standing Committee (16), there is no evidence so far in the international medical and lay press that such radical reform of the regulatory system is taking place. Further, the general mistrust of the Indian pharmaceutical sector as a whole has continued to increase (17,18,19). It is of paramount importance for India to

pursue regulatory reform and to let the rest of the world know of the progress in a timely manner, for at least three major reasons: (i) to ensure full protection of patients within and outside India, (ii) to rebuild a climate of trust and confidence with other regulators in the North and the South, and (iii) to create a positive model that could be adopted by other countries with a variable regulatory environment.

In a recent letter to *Developing Countries Bioethics* (20), Goyal argued that India should rise to the challenge and take proactive steps to alleviate the concerns regarding the standards of quality of its pharmaceutical market, so that it can retain its status as the “pharmacy of the world,” as well as fulfill its “moral responsibility” to supply quality, affordable medicines all over the world. We fully support this view – correcting the problem of variable pharmaceutical standards is primarily not a technical problem, but an ethical imperative, linked to the principles of beneficence and non-maleficence. The moral responsibility of “not harming” individuals who are receiving medical care does not concern only those who have a direct relationship with the patient (doctors, nurses, pharmacists, laboratory technicians, etc.), but also all those whose activities may have a positive or negative impact on the patient’s safety and protection, including pharmaceutical regulators, manufacturers and distributors. Universal access to quality-assured medicines is a necessary prerequisite for beneficence and for justice in access to health.

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