How a tragedy became a catalyst for sustainable improvement in medicine safety

Fatal incidents due to the use of substandard and falsified medicines still frequent the news headlines.[1] Such events should be a catalyst for efforts to improve medicines' regulation, manufacturing, management, and surveillance in every country. Here we share an example of a "build back better" initiative that led to the successful transformation of pharmaceutical industry standards in Pakistan.

In December, 2011, patients began presenting to public hospitals in Lahore, Pakistan, with unexplained bleeding and dark spots on the skin, diagnosed as bicytopaenia.[2] More than 200 deaths and more than 1000 cases were eventually reported. Having eliminated several possible causes, including dengue haemorrhagic fever, clinicians suspected that the symptoms were a result of an adverse drug reaction. An analysis of the patients, their demographics, and their medication revealed that they had all received free medicine from the Punjab Institute of Cardiology (PIC) in Lahore. The pharmacy records of the PIC outpatient department showed that between Dec 10, 2011, and Jan 11, 2012, 46 000 patients were dispensed a combination of aspirin, atenolol, amlodipine besylate, isosorbide-5-mononitrate, simvastatin, and clopidogrel.

As none of these medicines used for treatment of cardiac illnesses contained ingredients that would cause bicytopaenia, attention shifted to the possibility of falsified or contaminated medicines. Tablets retrieved from bicytopaenia-affected patients, the families of the deceased, and the PIC pharmacy store were analysed in Pakistan, the UK, the USA, and France, coordinated by WHO in Pakistan and at Geneva Headquarters. The implicated medicine was identified by a rapid fingerprinting method using nuclear magnetic resonance spectroscopy at the UCL School of Pharmacy in the UK. One batch of the anti-angina drug isosorbide-5-mononitrate (brand name Isotab) was found to contain a significant quantity of an unknown agent in addition to the active ingredient. Forensic analysis by the UK Medicines and Healthcare Products Regulatory Agency identified the unknown ingredient as the antimalarial drug pyrimethamine; each tablet contained 50 mg thereof. A daily dose of two to three contaminated Isotab tablets would have provided approximately 14 times the dose required to treat malaria. The cause of the unexplained deaths was confirmed as a single batch of contaminated Isotab-20 tablets, manufactured in Karachi and procured by PIC in Lahore. This link was also confirmed by the consequent postmortem analysis of blood and urine of deceased patients.[3]

Lahore's Chief Minister's Office was informed, and folinic acid, an antidote identified by haematologists at the Royal Free Hospital, London, UK, was administered to surviving patients affected by the contamination, who recovered rapidly. There was a national recall of Isotab batch J093 tablets, which was announced in the media.[4] WHO carried out a gap analysis which highlighted the need for the Drug Regulatory Authority of Pakistan to be reformed centrally and that many quality control laboratories across the provinces had not obtained accreditation nor met international standards (ISO 17025) or WHO prequalification requirements.

WHO Pakistan identified International Health Partners (IHP)—a UK-based non-governmental organisation that had worked in Pakistan since 2005—as a partner to collaborate with the Federal and Punjab Ministry to provide support and expertise to strengthen the quality control laboratories. Despite the dedication and competence of the laboratory teams, the comprehensive gap analysis identified a shortage of essential equipment, funding for overheads, training for analysts and technicians, quality management systems, and management infrastructure. The project lead at IHP and a quality management system expert used the WHO gap analysis to focus on identified key areas and develop the resources, processes, and systems required to be put in place.

Building on the work by the IHP project lead and the WHO actions, the US Pharmacopeia's Promoting the Quality of Medicines (PQM) programme was contracted to build a sustainable regulatory, quality assurance, and quality control system for the Drug Regulatory Authority of Pakistan at federal and provincial levels. This programme helped the quality control laboratories in Pakistan to operate in compliance with internationally acceptable standards of practice. The PQM/PQM+ programmes also provided technical assistance to strengthen the Drug Regulatory Authority of Pakistan's capacity to achieve the WHO Global Benchmarking Maturity Level 3, with

***Panel:* Outputs of the Drug Regulatory Authority of Pakistan's reform efforts**

- The Drug Regulatory Authority of Pakistan became ISO 9001:2015 certified in 2019
- At least 11 quality control laboratories achieved international recognition, of which seven achieved ISO/IEC 17025:2017 accreditation and five attained WHO Prequalification
- In 2020, Gilead awarded a manufacturing contract for remdesivir—a putative treatment for COVID-19—to a Pakistani manufacturing company, Ferozsons[5]
- In 2021, the Promoting the Quality of Medicines Plus programme assisted the Drug Regulatory Authority of Pakistan in developing guidance on emergency use authorisation of medical devices, trained national quality control laboratory analysts on COVID-19-related medical product testing, and supported the Institute of Public Health Diagnostic Laboratory to achieve ISO 15189 certification[6]
- In 2023, the first oral zinc solution in the world, prequalified by WHO,[7] was produced in Pakistan, as well as a dispersible zinc tablet, as a result of technical assistance from the Promoting the Quality of Medicines Plus programme

a primary focus on improving its product registration, inspection, and licensing process and procedures, through the introduction of an integrated regulatory information management system. More than 1000 Drug Regulatory Authority of Pakistan staff and pharmaceutical manufacturer personnel were trained in various quality assurance and control aspects of medicines. This resulted in a number of remarkable outputs (panel).

The tragedy that occurred in Lahore's public hospitals in early 2012 led to a comprehensive root cause analysis that revealed flaws in the systems for regulation, manufacturing, and analysis of medicines. The judicial commission established by the High Court in Lahore to investigate stated in December, 2012, that "this report should act as an eye-opener for all concerned who must take immediate steps to implement existing laws in letter and spirit, introduce fresh legislation where required, frame new rules and regulations, put in place efficient, effective and modern systems and administrative structures as suggested herein so that the lives lost in this tragic incident would not have been lost in vain".

Every country must develop the medicines regulatory and manufacturing knowledge and skills required to ensure that their citizens only receive safe and effective medicines; poor manufacturing standards must be eliminated.

MZ was provided study material that comprised tablets collected from patients and stores and was paid for the nuclear magnetic resonance spectroscopy analysis by the Government of Punjab, Pakistan, in January, 2012. The other authors declare no competing interests.

The success of this programme is the result of international collaboration of many global and local experts, including Mick Deats (Retired, WHO Substandard and Counterfeit Medicines Team); the WHO Regional Office for the Eastern Mediterranean; the High Court of Lahore; the UK Medicines and Healthcare products Regulatory Agency (MHRA) and its analytical laboratory; the USAID-funded Promoting the Quality of Medicines programmes; the US Pharmacopeial Convention; haematologists at the Royal Free Hospital, London, UK; the UK National Health Service Poison's Centre; the Essential Medicines Team in WHO (Geneva and Pakistan); Emma Hancox (quality management system expert); the Pharma Bureau Pakistan; and the Pakistan Pharmaceutical Manufacturers' Association.

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