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Routine quality control of medicines in developing countries: Analytical challenges, regulatory infrastructures and the prevalence of counterfeit medicines in Tanzania

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ABSTRACT

Counterfeit and substandard medicines still constitute a worldwide problem and do not only affect health-care systems in low and middle income countries but also in the industrialized world. Whereas in the developed world the quality of pharmaceutical preparations is assured by a dense network of quality control laboratories utilizing modern analytical techniques the situation is completely diverse in resource constraint countries. Implementing full monograph testing according to the American or the European Pharmacopoeia represents an extreme challenge. The respective quality control organs easily become overburdened and face central problems when supplying immaculate medicines. This review collected information on the prevalence of counterfeit and substandard pharmaceuticals in Tanzania and discusses suitable analytical approaches for their analysis, e.g. non-sophisticated HPLC, low-field NMR, capillary electrophoresis, or vibrational spectroscopy. Due to the limited validity and reproducibility of field assay kits like the Minilab® the impact of precise, simple, and robust analytical methods is highlighted.

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Abbreviations: API, Active Pharmaceutical Ingredient; EDQM, European Directorate for the Quality of Medicines and HealthCare; GMP, Good Manufacturing Practices; IPC, In Process Control; LF-NMR, Low-Field NMR spectroscopy; MEDS, Mission for Essential Drugs and Supplies; NMRA, National Medicine Regulatory Authority; OMCL, Official Medicines Control Laboratory; Ph. Eur, European Pharmacopoeia; PMS, Post Marketing Surveillance; QC, Quality Control; TFDA, Tanzania Food and Drugs Authority; USP, United States Pharmacopoeia; WHO, World Health Organization.

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1. Introduction

The term "counterfeit and substandard medicines" describes a phenomenon which has been extensively studied and reported in the past. The provision of good quality medicines and pharmaceutical preparations, respectively, represents the backbone of every health care system worldwide: ensuring their availability is crucial for effective treatments and life saving therapies [1]. As the dispensed amount of e.g. an antibiotic agent is a very sensitive parameter, administering substandard medicines delays the therapeutic success, generously triggers the manifestation of resistances, and generates even more devastating burdens for the already weakened health systems [2–4]. In countries of the developing world a comprehensive quality monitoring of circulating medicines is barely possible due to relatively young health care systems, restricted laboratory capacities, weak analytical infrastructures, and chaotic distribution logistics. On the other hand, in the industrialized parts of the world the falsification of extremely expensive biotechnologically produced APIs, lifestyle medication, traditional herbal medicines and dietary supplements has become more and more relevant [5–10], indicating that the counterfeit problem is not exclusively limited to low and middle income countries any more [5,11]. However, the majority of cases remains affiliated with those countries, e.g. in sub-Saharan Africa, where antibiotic, antiparasitic, and antiretroviral medicines are highly affected by pharmaceutical counterfeiting [11,12]. This is very tragic because they demand for huge amounts of anti-infectives which must be available in good quality [2,13–15]. The real extent of the problem can hardly be estimated, as a high percentage of such affairs remains undiscovered.

Evaluating the quality of active pharmaceutical ingredients (APIs) and excipients, respectively, is an integral part of contemporary pharmaceutical quality control (QC) and Good Manufacturing Practices (GMP) [16]. Usually a broad variety of modern analytical methodologies which allow the quantitative determination of the content and the purity of the API are being applied. Separation techniques like thin layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography (GC), and capillary electrophoresis (CE) are fully established and have been added to almost all monographs of the major pharmacopoeias, e.g. the European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopoeia and the United States Pharmacopoeia (USP) [17,18]. Sophisticated spectroscopic methods like infrared (IR), near infrared (NIR) and Raman spectroscopy, nuclear magnetic resonance (NMR), and mass spectrometry have additionally gained a lot of attention within the last decades [19,20]. Hyphenating the respective separation and detection techniques allows for drawing a very detailed picture of an analyte or an analyte mixture. The structure of new or unknown contaminants can be elucidated and determined even in very small quantities [21]. In modern quality control laboratories this huge inventory of analytical technologies is available anytime, a fact which allows an extensive product testing during production and during the distribution within the respective supply channels. This is only possible because the respective facilities have distinct features being obligatory to run modern instruments and which are not necessarily being found in every laboratory at anytime, e.g. air conditioning, running water and water purification systems, or electricity.

Although National Medicine Regulatory Authorities (NMRAs) have been implemented in almost all developing countries only few of them can be considered as being fully functional and operational, while others are at different levels of establishment. They suffer from a constant overburdening due to lacking resources, weak infrastructures, and the great workload which is due to the high turnover of medicines [22]. The Tanzania Food and Drugs Authority (TFDA) in Dar Es Salaam may be seen as one of the most advanced medicine regulatory authorities in sub-Saharan Africa. However, it is still a very young institution which is operating in a rather centralized manner (see Table 1).

2. Types of poor quality and adulterated/counterfeit products

Several definitions of counterfeit medicines exist, however the explanation of the World Health Organization (WHO) can be seen as the most elaborate which has gained a lot of international acceptance. Falsified medicines are described as "deliberately and fraudulently mislabelled with respect to identity and/or source, with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging" [11]. An alternative may be using the expression "spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines".

In general the following five categories have to be distinguished:

i. Copies of genuine brand medicines, often with correct amounts of the API;
ii. Products with wrong APIs; they may be of poor or of acceptable quality;
iii. Preparations containing no API at all;
iv. Medicines with too high or too low contents of the declared API;
v. Contamination with known and/or unknown impurities.

It may not always be possible to discretely assign a sample to one of these five subtypes. Non-conformance to GMP standards may result in the production of low quality products not meeting the respective quality requirements. One of the most common practices is the manufacture of placebo formulations not containing the declared API [23]. In addition, counterfeiters may not manufacture new products, but repack, relabel and resell authentic medicines after their original shelf life has expired.

3. The quality control of medicines in developing countries: challenges, limitations and analytical techniques being suitable for routine application

3.1. Challenges and limitations

Whereas in the industrialized world all sectors of the medicine market as well as the regulatory frameworks are highly controlled by internationally harmonized standards we may find a completely inverse situation in almost all poorly developed countries. Routine investigation of the quality of medicines demands for a highly connected network of qualified testing laboratories which are able to apply a broad spectrum of analytical techniques. In contrast, in developing countries adequately trained personnel may not be available at all, as well as the necessary apparatus, the required chemicals and reagents. This is either due to the unaffordability or logistic restrictions hindering the effective distribution of the respective items. It is not uncommon that spare parts have to be imported and that their delivery takes up to several months. Unpredictable power breakdowns, extremely elevated temperatures and air humidity, and shortages in the supply of consumables or chemicals constitute only few reasons why almost all modern analytical instruments cannot be run in daily routine. As a consequence the quality control of medicines is either being performed in a handful of centrally located, prequalified testing laboratories which are heavily suffering from the resulting workload or is directly outsourced to foreign countries. Both aspects hinder continuous investigations, are responsible for unexpected additional costs and pose enormous logistical challenges.

Since only a few laboratories in developing countries are able to meet international quality and laboratory standards, in 2001 the WHO introduced a qualification programme where testing laboratories, manufacturers, and their respective products and services are being