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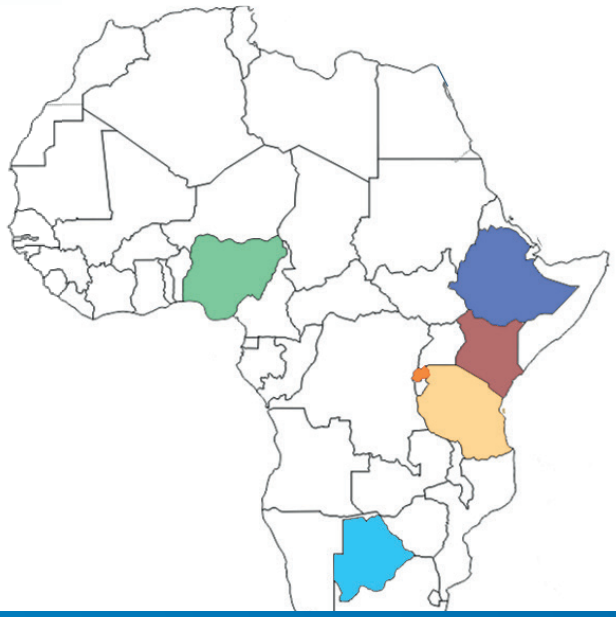

Lucie Moeller
with the collaboration of Peter Imming and Eliangiringa Kaale

Drug Lifecycle Control in Sub-Saharan Africa

Book of Abstracts
to the Workshop Drug lifecycle control in Sub-Saharan Africa - From production to responsible safe disposal and elimination in wastewater treatment plants

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Book of Abstracts

to the workshop „Drug lifecycle control in Sub-Saharan Africa - From production to responsible safe disposal and elimination in wastewater treatment plants (Med4Africa)“

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Project leaders:
Department Centre for Environmental Research, Helmholtz Centre for Environmental Research (UFZ)
Institute of Pharmacy, Martin Luther University Halle-Wittenberg (MLU)
School of Pharmacy, Muhimbili University of Health and Allied Sciences (MUHAS)

Editors:
Dr.-Ing. Lucie Moeller
with the collaboration of Prof. Dr. Peter Imming and Prof. Dr. Eliangiringa Kaale

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Introduction

The circular economy shows the need of observing products in their entire lifecycle - from the production to their fate after the use. Pharmaceuticals are primarily a means of saving lives and ensuring the well-being of people and animals. However, what is the fate of the used pharmaceuticals that are not metabolized and are therefore released into the nature? And, what happens with them if they expire without being used? Is there any possibility to include pharmaceuticals into the circular economy and use the expired drugs as a resource? Would this way be one of the solutions to enhance the resilience of Sub-Saharan Africa in regard to drug shortage due to missing production facilities and their dependency on markets from other continents?

To discuss these and more questions in detail from the perspectives of the drug development, production, safe use, responsible disposal, and possible reuse, more than 30 professionals working in universities, government agencies, control laboratories, hospital pharmacies and manufacturing pharmaceutical companies from seven countries (six Sub-Saharan countries - Tanzania, Ethiopia, Botswana, Kenya, Nigeria, and Rwanda – as well as Germany) met in a workshop with the title “Drug lifecycle control in Sub-Saharan Africa - From production to responsible safe disposal and elimination in wastewater treatment plants”. The workshop took place in Arusha (Tanzania) in September 2022 and was financed by the Volkswagen Foundation in frame of the initiative “Knowledge for Tomorrow – Cooperative Research Projects in Sub-Saharan Africa”. In addition to numerous lectures on topics related to the overarching topic of "Drug Lifecycle Control", there was also a practical part on the use of simple technologies to determine the active ingredient content of drugs. Such technologies also complement the Global Pharma Health Fund (GPHF) Minilab, the use of which was demonstrated on site at the central drug control laboratory in northern Tanzania. A large part of the workshop was devoted to planning which research projects could be specifically addressed from among the participants.

This UFZ report involves the abstracts of the talks of the workshop the presentation of which are presented on the website “www.ufz.de/med4africa”. The aim of this report is to provide a brief overview of the issues that have been discussed and need to be discussed further in regard to pharmaceuticals in relation to the circular economy in (but also outside of) Sub-Saharan Africa.

1 Production of Active Pharmaceutical Ingredients and Excipients

1.1 Introduction to the Production of Active Pharmaceutical Ingredients and Excipients

Peter Imming, Andreas Beuchel

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany, e-mail: andreas.beuchel@pharmazie.uni-halle.de

In recent years, it has become evident that access to medicines is highly dependent on global supply chains. The outbreak of the Covid pandemic demonstrated that diversification of production locations makes the supply of essential medicines more resilient to crises. In addition, regional pharmaceutical production has the advantage of shorter supply routes and the ability to adapt to specific local needs. Based on these considerations, possibilities and limitations to the expansion and establishment of the production of active pharmaceutical ingredients (APIs), excipients and drugs in Sub-Saharan Africa (SSA) are discussed.

The conditions in SSA result in special challenges for pharmaceutical companies to be successful. Pharmaceutical production requires a well-developed infrastructure for the region in which it is located. Mandatory access not only to APIs, but also to pharmaceutical excipients and packaging materials limits the locations suitable for such companies. For APIs, a few countries dominate production worldwide (PR China, India) [1]. Therefore, to be economical, API must be competitive with importing countries. A major opportunity for SSA is the development of active ingredients based on natural material from traditional African medicine. In detail, it seems promising to focus on the production of anti-infectives, which are produced in only a few locations worldwide. However, converting a natural substance into an active drug ingredient is a time-consuming research process.

Initially, a molecular target must be defined and an active agent identified. There are two different approaches to finding an active agent. The classical approach starts with the development of preclinical drug candidates, followed by a clinical phase to determine tolerability, dosage and efficacy. In contrast, reverse pharmacology relies on clinical observations and biodynamic effects of traditionally used medicine. Based on these data, experimental studies are conducted to evaluate target activity. Finally, the results are used to develop new lead compounds. Reverse pharmacology has the potential to shorten the time to produce a promising drug candidate. Because safety and tolerability have already been demonstrated through traditional use, the occurrence of toxicity during the development process is less likely [2]. While the discovery of biological activity is the most difficult part, the subsequent analysis of pharmacokinetic data is a bottleneck in this development process.

Natural products are a rich source for identifying promising hit substances that can then be modified by medicinal chemistry in an iterative process. The development of a hit compound into a lead structure for the clinical phase involves the assessment of important pharmacological parameters such as permeability, microsomal stability or bioavailability. Furthermore, since certain drugs are potentially harmful to the environment and human health if they accumulate in ecological systems, it is desirable to screen a potential drug candidate for ecotoxicological effects, although this is not currently mandatory. There are also concepts for the development of biodegradable derivatives of approved drugs with an equivalent pharmacological profile [3].

Once a substance has been approved, it is however questionable whether it can be produced on a large scale. With a view to unproblematic processing and optimum shelf life, the substance should be in a solid state and exhibit sufficient chemical stability even at relatively high temperatures. The synthesis of a commercially successful compound should be short and without the use of heavy metal catalysts to reduce toxic waste. Estimates suggest that it is presently hardly possible to newly set up API in both Europe and SSA because only a few of the necessary starting materials are available. In addition, foreign companies benefit from low production costs, which makes it difficult to compete with them [4]. Considering these facts, it is evident that active ingredient production is a less favorable business model than drug formulation. Since many countries in SSA already have factories for the production of drug formulations, there is an opportunity to expand this industry [5]. This opens up the possibility of introducing modern production techniques to increase production capacity and reduce costs.

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1.2 Resources needed and chemical methods used in current active pharmaceutical ingredient (API) synthesis

Peter Imming

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany, e-mail: peter.immingl@pharmazie.uni-halle.de

In 2019, McKinsey published a report on whether sub-Saharan countries should make their own drugs [1]. Five basic lessons can be distilled from this report. To be successful, African countries should (1) focus on quality, (2) carefully assess production capacity, (3) build regional hubs rather than national production sites, (4) embark on drug-product formulation rather than API production, (5) factor in value-chain effects. API production is very scale sensitive and would need substantial investment in precursor production plants. Since many API production sites and processes are relatively old, African countries could build modern API production because they need not supplant existing ones. Modern API plants would have to include improved process chemistry (cost reduction 5-35%), continuous manufacturing (cost reduction 10-25%), and modular plant design (faster construction of the plants). However, policy-makers need to understand: (1) modern API factories are heavily robotized, so they do not create many jobs, (2) API production accounts for only 10% of the total cost of e.g. tablets. So again, drug formulation is a better economic bet.

APIs need to have certain physicochemical features such as crystallinity, short synthetic pathway, solubility, bioavailability, nanomolar activity [2]. Before they are suitable as drug susbstances, natural products usually need to be modified semisynthetically for better stability during storage and in metabolism. Modern synthetic APIs typically show modular constitution which is due to current synthetic strategies and constraints. For instance, the anticoagulant rivaroxaban and the antibacterial drug linezolid look very much alike. While current drug synthesis relies on a relatively low number of chemical building blocks and organic chemical transformations [3], creating an API production industry would need very costly long-term investment in personnel education - academic and vocational - and factories, not to forget ways to depose of inevitable synthetic side-products (chemical waste).

Since most APIs are presently produced in very few countries (India, P.R. China, Mexico), an anlysis of what it would need for Germany and Europe - that lost most of its API production capacity in the past decades - to produce APIs has bearing on related considerations in Africa. For an API like hydroxychloroquine sulfate, used against malaria and chronic rheumatic diseases, Germany is eight synthetic steps away from preparing the API, nitrobenzene being the "earliest" starting material in a standard synthesic process. Focussing on the economic rather than technical situation of API production in Europe, a study [4] showed that the total value (manufacturers' price) of antibacterial cephalosporins amounted to 110 million € in Germany 2017 on the basis of 100 tons sold per year. The production of cephalosporins needs

fermentation of *Cephalosporium* species, cornsteep, fish and meat meal, two enzymatic hydrolysis steps, and a number of chemical processes. Even for the approx. 500 tons of cephalosporins used in the Europan Union presently, representing a value of 125 million €, production would not be ecomomic. Production sites in e.g. Bangladesh, owned by Chinese companies, benefit from scale effcts, low labour costs and amortised production facilities.

It will need for "the Lord to build the house" [5] to overcome the situation aptly described by Barthélemy Nyasse [6]: "37 [African] countries have some pharmaceutical production, and only South Africa has limited primary production of active pharmaceutical ingredient (API) and intermediates. ... With the partial exception of South Africa, production in sub-Saharan Africa is generally limited to final formulations, characterized by non-complex, high-volume essential products, encompassing basic analgesics, simple antibiotics, anti-malarial drugs, and vitamins."

In closing, it is suggested that (1) APIs are identified that are synthetically relatively easy to access, serve a particular need and are of low interest to the "big players" in API production; (2) go for antiinfective APIs that are produced by 1-2 companies only worldwide at present.

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1.3 How to Turn a Natural or Synthetic Compound into a Drug Substance

Andreas Beuchel

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany, e-mail: andreas.beuchel@pharmazie.uni-halle.de

The development of a new drug is a multidisciplinary approach that can be divided into three main steps: medicinal chemistry research, clinical phase and approval/marketing. The first step consists of the discovery of an active compound and its development into a preclinical lead compound. Specifically, the process involves testing to determine a number of key pharmacological parameters employing in vitro and in vivo models. In parallel, chemical derivatization is used to shape the pharmacological profile of drug candidates (Fig. 1). Natural product chemistry provides a rich source of pharmacophores and enables drug complexity that could not be achieved by chemical synthetic approaches alone. Therefore, the in-depth study of medicinal plants and materials used in African traditional medicine could reveal undiscovered active compounds as starting points for new drug development.

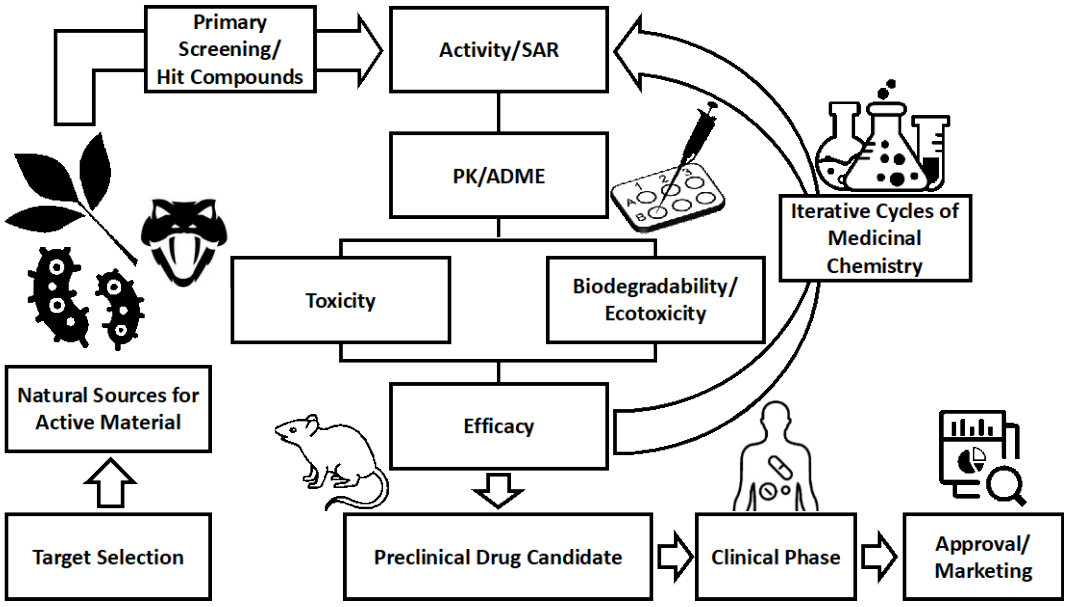

Figure 1: Drug discovery and preclinical development. The scheme depicts the main steps of the process from the discovery of an activity to the clinical phase. All steps are supported by medicinal chemistry to reshape the respective parameters. SAR structure-activity relationship; ADME absorption, distribution, metabolism and excretion of a drug.

In addition to the identification of active compounds with functional activity, the optimization of their pharmacokinetic properties is the bottleneck in the drug development process (for an example of our own work, see [1]). The ultimate goal of pharmacokinetic improvement is an active compound with good oral bioavailability, as this is the primary route of administration.

To achieve this, potential drugs must have sufficient solubility in physiological media, permeability for cellular uptake, and metabolic stability to prevent inactivation. A widely used approach to affect the permeability of a lead compound is the formation of prodrugs. Prodrugs are derived from biologically active molecules and represent a precursor that is converted into its active form by in vivo metabolization. For example, esters are rapidly hydrolyzed after absorption, releasing the active carboxylic acid [2]. Bioisosteric substitution, i.e., the replacement of critical structural parts with those having similar biological effects, represents another approach to modulate bioavailability or enhance the activity of a drug molecule. Carboxylic acids are widely used in natural products. They are rapidly excreted by acyl glucuronidation or acyl-CoA thioester formation, the latter of which can cause side effects. These disadvantages are avoidable if the acid is replaced by a tetrazole. A prominent example of this technique is the development of angiotensin II receptor antagonists (e.g., losartan) [3]. Although molecules must be stable enough to exhibit an in vivo effect, it is important to consider that certain compounds accumulate in the environment or form toxic metabolites. Intelligent drug design and routine biodegradation testing offer the opportunity to anticipate the development of a drug that could be harmful to ecological systems. Attempts have already been made to chemically modify approved drugs to improve their biodegradability without compromising their pharmacological activity [4].

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2 Development of quality herbal medicines in Tanzania: Opportunities and Challenges

Mainen Julius Moshi[1], Alphonce Ignace Marealle[2], Ramadhani Selemani Omari Nondo[1]

[1]Department of Biological and Preclinical Studies Muhimbili University of Health and Allied Sciences, Box 65001 DSM, Tanzania, e-mail: gynura1955@yahoo.com

[2]School of Pharmacy Muhimbili University of Health and Allied Sciences, Box 65001 DSM, Tanzania

Traditional medicine practice (TMP) is deeply integrated into Tanzanian cultures and it is the most common form of healthcare. The Government of Tanzania enacted the Traditional and Alternative Medicines Act 2002 with the ultimate goal to integrate TMP into the healthcare system.

Tanzania boasts of over 12,000 endemic plant species, a number of which are used in TMP, but only about 5,000 medicinal plant species have been documented and no monographs are developed. Therefore, Tanzania stands in a weak position in prospects to easily develop standardized herbal medicines. A number of plants used in Tanzanian TMP appear in the WHO monographs, West African, Indian and Chinese herbal Pharmacopoeia which information could be adopted as the starting point towards standardized products development.

Different stakeholders are involved in traditional medicines research, including the Sokoine University of Agriculture, the National Institute for Medical Research, the Department of Chemistry University of Dar es Salaam, the Institute of Traditional Medicine (MUHAS) and the Ifakara Health Institute extending from phytochemistry, ethnomedical, and pharmacological studies; a few clinical trials, and preclinical toxicology.

Progress has been made in bioassays and bioassay guided isolation of antiplasmodial [1,2], anticancer [3], antimycobacterial [4], antifungal compounds and others and momentum is growing in the conduct of preclinical studies, clinical trials and formulation of herbal medicines. Capacity building in the standardization of herbal products is in progress. However, loss of medicinal plants in the form of illegal timber, expansion of human settlements, agricultural activities, forest fires, tree felling for timber, international trade, and refugee activities constitute a big challenge, therefore any meaningful industrial production of herbal medicines must be supported by cultivation of the medicinal plants.

The future for production of quality herbal medicines in Tanzania requires interventions including development of monographs, enhanced capacity for safety and efficacy evaluation, capacity for synthetic chemistry, and capacity for standardization of TMPs. Intersectoral collaborations are necessary to strengthen legislations on management of medicinal plants biodiversity, and building of commercial farming for medicinal plants. Building capacity for patenting and registration of herbal medicines, and managing supply chain with respect to

active pharmaceutical ingredients and Finished Pharmaceutical Products and establishing a strong linkage between industry and academia are much needed.

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3 Drug manufacturing

3.1 Summary of the Discussion of Drug Manufacturing

Karsten Mäder

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany, e-mail: karsten maeder@pharmazie.uni-halle.de

The participants of the discussion group drug manufacturing started the discussion with the analysis of the current situation. There was common agreement between the participants, that Drug manufacturing covers aspects of the synthesis or extraction of the bioactives (drug molecules), the formulation development and manufacturing but also aspects of the fate of the medicine after administration to the patients. They concluded, that the current situation is not satisfying with regard to the following aspects: (1) environmental aspects of drug manufacturing, (2) efficacy and variability of pharmacokinetics and (3) local capacities for drug manufacturing.

The participants agreed that both synthetic drug molecules and nature derived drugs are important. Both for drug synthesis and drug extraction from plants, environmentally friendly procedures should be used and the use of organic solvents should be minimized. The participants agreed that supercritical carbon dioxide is an environmentally friendly option to achieve this goal. It can be used both for the extraction of bioactives from plants but also for the formulation of nano- or microparticles. This method is already established in the pharmaceutical industry, but scarcely used in Africa so far. Environmental aspects should also be considered in the production of the pharmaceutical dosage form. Again, organic solvents should be avoided and environmentally and energy friendly procedures should be used. Continues processes should be preferred over batch production. Extrusion technologies and electrospinning have been recognized as promising technologies.

A major problem in the treatment of malaria and other tropical diseases is the high food dependency of drug absorption after oral administration. Currently, some products exhibit a food dependency of 16 times (comparing fed state to fasted) which causes a lot variability and lack of efficacy. Efforts should be strongly increased to raise the awareness for this problem and to educate young researchers in theory and practice how this problem can be tackled.

Finally, it was recognized that capacities within Africa should be strengthen and increased to develop the pharma industry in Africa. The participants agreed to work together closely and to cooperate in the form of the organization of workshops, the joint supervision of PhD-students and joint project with clear focus on clinical translation.

3.2 Formulation of antimalaria drugs: challenges and solutions

Karsten Mäder

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle, Germany, e-mail: karsten.maeder@pharmazie.uni-halle.de

Common problems with antimalaria drugs include low and highly food dependent oral absorption, rapid metabolism and excretion and low storage stability. For example, the AUC of Lumefantrine of the marketed product Riamet® increases 16-fold compared the fasted state [1]. The administration requires therefore the intake of food. However, the impact of food on oral absorption enhancement will highly depend on the food and the patient itself. It is therefore highly desirable to develop formulations which minimize the food effect on oral absorption of antimalarial drugs. The formulations should also be simple and cost effective to produce and have high physicochemical and chemical stability. An understanding of the drug properties is the starting point in the rational development. Possible strategies for dissolution enhancement include lipid-based drug delivery systems, amorphous systems, complexation with cyclodextrins, pH adjustment and salt formation. Lipophilic molecules, such as Lumefantrine and Artemisinins are good candidates for the development of lipid-based drug delivery systems. We focused on the development of self-microemulsifying drug delivery systems (SMEDDS) for Artemisone and developed a formulation with high stability and efficacy against schistosomiasis [2] and malaria [3,4] in preclinical studies. The formulation is produced by simple mixing of the drug with the SMEDDS forming excipients. The SMEDDS formulation is thermodynamic stable and can be administered orally, transdermal, via injection or pulmonal. Because of the high absorption efficacy, a much smaller dose is required compared to previous formulations. Our data also show that artemisone is more effective compared to Artesunate [4].

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3.3 Steps and Considerations in the Galenical Development to Commercial Production of a Pharmaceutical Drug Product

Reinhard Walter

Industry Pharmacist, Germany, e-mail: dr.reinhard.walter@web.de

The planning of the development of a drug product requires multiple considerations around the active pharmaceutical ingredient, to assure safe and effective administration of the drug. Based on the best route of administration and best patient compliance assessment the delivery form is selected. The formulation work has to consider not only medical and technical properties but regulatory and market specific requirements. Formulation ingredients and packaging material are selected to achieve the highest level of compliance with all requirements. The quality target profile is the guidance through all galenical formulation stages and should be continuously updated to reflect the learnings.

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3.4 Manufacturing skills building in Africa: Experience from Nigeria

Chinedum Peace Babalola[1,2], Adewale M. Adeyemi[1], Olayinka A. Kotila[1]

[1]Centre for Drug Discovery, Development and Production (CDDDP), University of Ibadan, Ibadan, Nigeria, e-mail: peacebab@gmail.com

[2] Chrisland University, Abeokuta, Nigeria.

Africa bears a quarter of the world's disease burden yet consumes less than 2% of pharmaceutical products. Nigeria, which is the Sub-Saharan nation with the largest population only boasts of four pharma companies with WHO prequalification status, lacks inputs and infrastructure from the government to support production locally, is devoid of well-trained personnel to undertake manufacturing projects in pharma industries and faced with challenges of high cost of pilot medicine projects on a production scale. These gaps call for an intervention, which academia can fill.

We set up a team of drug experts and applied for a funding opportunity that enabled the institution of the Centre for Drug Discovery, Development and Production (CDDDP), University

of Ibadan. The Centre's approach is a novel marriage of academia, regulatory and industry with key objectives that include, establishing short- and long-term training programmes on drug development and regulation, translating research findings to finished products, and providing oversight functions in bioequivalence and clinical trials.

In 2011, the team won a MacArthur Foundation grant of $950,000, established two postgraduate degree programmes in drug development, production and medicine regulation. The Centre has graduated three sets of Postgraduate Diploma students in Drug Development comprised of seventeen (17) females and fourteen (14) males. Fifteen (15) of them are from pharmaceutical industries, eleven (11) from academic institutions and five (5) from other sectors. The Masters in Drug Development and Regulatory Pharmacy Programme commenced with twenty (20) students, four (4) of whom were pioneer students of the Centre. Four workshops and two international conferences have successfully been held. The Director General of the national drug regulatory agency of Nigeria graced one of them. The Centre has to her credit production and ownership of herbal teas, alcohol-based sanitizers, and antimicrobial cream and anti-COVID-19 remedy. The Centre maintains collaborations/partnerships with Howard University, Purdue University both in the USA, Reckitt Benckiser (Europe), BASF, AiBST Zimbabwe, to mention a few. CDDDP houses a state-of-the-art laboratory for quality assurance of medicines and has anchored over one hundred (150) graduate research projects from both within and outside the University of Ibadan. It offers third-party analyses to pharmaceutical companies, has undergone auditing in preparedness for WHO pre-qualification, and has established standard operating procedures in line with global standards. In 2014, CDDDP attained the status of Regional Centre of Regulatory Excellence (RCOREs) in Africa by the African Medicines Regulatory Harmonization (AMRH) programme under the New Partnership for African Development (NEPAD). Presently, CDDDP is a core-Flex partner with the United States Pharmacopeia under the USAID-sponsored Promoting Quality of Medicines Plus (PQM+) in LMICs. We are currently in a phase of train-the-trainers so that subsequently the Centre will engage in capacity development of pharma industrial and regulatory personnel in quality management systems. The centre is also promoting capacity building in computer-aided drug design (CADD)

The successful conceptualization, development and recorded milestones achieved by the Centre for Drug Discovery Development and Production establishes the entire process as one that can be adopted as template by other regional institutions of learning as a viable tool towards strengthening of pharmaceutical systems and ensuring circulation of good quality drugs in the continent. Future goals include attainment of ISO 17025 certification status, establishment of a bioavailability/bioequivalence facility and development of novel formulations and drug delivery techniques.

4 Drug quality control

4.1 Introduction to Drug Quality Control in Sub-Saharan Africa

Vicky Peter Manyanga

School of Pharmacy, the Muhimbili University of Health and Allied Sciences, P.O. Box 65545, 11103, Upanga West, Dar Es Salaam, Tanzania, e-mail: vmanyanga@ymail.com

Even though drug development in Sub-Saharan Africa is still in its infancy, pharmaceutical Quality Control (QC) laboratories are well established in the majority of countries in this region. These QC labs have been established at different paces to cater for different needs across the SSA, such as National QC labs (National Medicine Regulatory Authority/National Bureau of Standards), Research and Development Laboratory (Universities/faculty/School of Pharmacy) and Pharm Industrial QC labs. The QC labs are mainly involved in routine/release sample analysis using pharmacopoeia and in-house methods, contract analysis, analytical method development and validation, stability studies as well as post-marketing surveillance analysis. To validate the trueness of data generated by these QC labs, they from time to time participate in a proficiency testing (PT) scheme which is organized locally by MUHAS Pharm R&D Laboratory (ISO 17043:2012 accredited) for the EAC region or other providers such as WHO EQAAS. It is important to note that some of the QC labs have been ISO 17025 accredited.

Quality control labs are a very crucial infrastructure in generating quality data for regulatory approval of medicines. However, there is number of challenges facing local manufacturers in Sub-Saharan Africa. The majority of local pharmaceutical industries have not invested in R&D labs due to high investment and running costs involved with little or no financial return. Financial capital is the main challenge identified which leads to employment of unskilled and incompetent personnel, poor manufacturing practices and small-scale manufacturing. Quality data require a combination of qualified people, qualified equipment (maintenance and calibration), availability of reference standards and validated analytical methods. Moreover, it was observed that there is a lot of costs involved in manufacturing medicines in SSA as compared to Asian countries because all materials (API, excipients, container-closure system) are individually taxed during importation: (This differs between countries in Sub-Saharan Africa:)

Like any other part of the world, substandard and falsified (S/F) medical products are also found in Sub-Saharan Africa. The exact ratio differs from country to country; for example in Tanzania; falsified medicines are reported to be about 1 % while substandard is about 10 %. The presence of these S/F medical products in circulation signifies the need for continual monitoring of registered products in the market. The monitoring can take two-step approaches; tier 1, which involves screening tests and tier 2, which involve confirmatory tests using pharmacopoeial or other validated analytical methods. Several efforts have been put in place

to fight S/F medicines, such as the use of mini-labs (GPHF) in ports of entries (drugs have no borders) in countries like Tanzania to screen for these products. GPHF mini lab essentially utilizes colour reactions, disintegration and thin layer chromatography tests for analysis. Improvement of TLC using TLCyzer (mobile app) can also be employed during screening. Other fast and environmentally friendly techniques are represented by (handheld) Near Infra-Red (NIR) and Raman spectroscopy. They allow quick identification since they do not involve any prior sample preparation. Confirmatory tests are important for questionable results from tier 1 (minilab or NIR). However, there is a need of agreement regarding specifications set by different pharmacopoeias, which are normally used interchangeably by SSA countries.
Presently, none of the QC labs in Sub-Saharan Africa is involved in the analysis of drug residues in the environment (improper disposal of expired/unused medicines).

4.2 Challenges of generating Quality Analytical Data to support Regulatory Approvals in Africa

Eliangiringa Amos Kaale

School of Pharmacy, the Muhimbili University of Health and Allied Sciences, P.O. Box 65545, 11103, Upanga West, Dar Es Salaam, Tanzania, e-mail: elia.kaale@gmail.com

National medicines regulatory agencies have a substantial impact on the regulation of safety, quality, and efficacy of licensed medications across the world [1]. The agencies play significant roles in the regulation of manufacturing, importation, distribution and selling of medicines, prescribing quality standards, conducting a quality audit, inspection and pharmacovigilance, educating the general public on regulatory matters and ensuing of business permits to safeguard public health. However, to effectively attain regulatory goals, agencies require good, robust and quality data for regulatory approval [2]. Equally important, poor-quality data significantly affect decision-making in regulatory agencies [3]. Several kinds of literature, including [2] recorded the challenge of poor-quality data and their impacts in African countries' health care systems and regulatory agencies in particular [4].
Discovery (R&D) Pharmaceutical Industry on the African continent is still at infantry on development [5], and a lot of patronage and investment are needed. Although the majority of the pharmaceutical plants operating are generic manufacturers yet, a substantial formulation of R&D data is needed to enable the compilation quality part of the dossier for marketizing authorization. Domestic manufacturers lack a Formulation R&D Facility to conduct formulation trials [6]. This makes it difficult to conduct systematic pre-formulation studies, formulation development trials from Lab Scale trials (0-5 kg) and subsequent optimization using a contemporary design space approach. This is followed by upscaling to Intermediate Scale trials (Up to 50 kg) and technology transfer to industrial scale 500+ kg, and manufacturing

process validation. Lack of formulation development infrastructure, systematic formulation development, and Inadequate Testing infrastructure result in formulation Copy & Paste, which is always missing the understanding of process parameters. This manifest in insufficient data for the compilation of dossier sections 3.2.S.1 to 3.2.S.7 and 3.2.P.1 to 3.2.P.7 to support regulatory approval for domestically manufactured pharmaceutical.

Broadly speaking, developing quality data for regulatory approval is still a big challenge in Tanzania and Africa. Few studies have examined common deficiencies found in generic Finished Pharmaceutical Products (FPP) [7] and APIs [8] applications submitted for registration to the South African Health Products Regulatory Authority (SAHPRA) supporting observation. For instance, in Tanzania, the Tanzania Medicines and Medical Devices Authority (TMDA) annual reports for the past six (6) consecutive years (i.e., from 2015/2016 to 2020/2021) have shown a significant number of applications that were not approved for not meeting the established data quality standards (Annual Reports TMDA, 2016, 2017, 2018, 2019, 2020, 2021).

A study commissioned by BMGF in 2020 revealed that most of the products registered in Tanzania and Uganda have the BE data generated in India. Regulatory Approval requires meaningful analytical data for sound decisions. For Africa to improve/ensure the generation of quality analytical data to support regulatory approval, the following considerations have to be made; Infrastructure in investment, Analytical instrument qualification and calibration, Analytical method validation, manufacturing process validation, Investment in quality health care facilities and services including BE Contracted research organizations (CROs).

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4.3 Substandard and Falsified Medicines in Sub-Saharan Africa: Prevalence and Prevention / Detection / Response

Lutz Heide

Pharmaceutical Institute, Eberhard-Karls-University Tübingen, Auf der Morgenstelle 8, 72076 Tübingen, Germany, e-mail: heide@uni-tuebingen.de

Among the Sustainable Development Goals of the United Nations, Goal No. 3 is concerned with good health, and sub-goal No. 3.8 calls for access to safe, effective, quality and affordable medicines for all. Medicines of good quality are essential for achieving the desired outcomes in health care. However, substandard and falsified medical products remain a serious problem especially in low- and middle-income countries. For example, in 2019 falsified tablets were discovered in Cameroon which were labelled to contain the antihypertensive agent hydrochlorothiazide, but they contained not hydrochlorothiazide but the (undeclared) antidiabetic compound glibenclamide [1]. These falsified tables caused severe, in several cases fatal hypoglycaemia in the unsuspecting patients. In a further case, in Malawi extremely substandard misoprostol tablets were discovered which contained only 13 % of the stated amount of the active ingredient and were ineffective in the prevention and treatment of life-threatening postpartum haemorrhage [2].

WHO estimates a very high number of deaths to result from use of substandard and falsified medicines every year. However, surprisingly different figures have been published in the scientific literature about the prevalence of substandard and falsified medicines. Our own studies in Cameroon, the DR Congo and Malawi, investigating governmental and faith-based health facilities, private pharmacies and informal drug outlets, showed an average prevalence of 1.7% falsified and 15.6% substandard medicines [3]. Similar figures have recently been reported by Ozawa et al. [4].

There is an urgent need to harmonize the tolerance limits used in different studies to distinguish compliant from non-compliant samples, as the use of different tolerance limits (e.g. of different pharmacopeias) leads to very different percentages of samples classified as out-of-specification [3].

The COVID-19 pandemic has exacerbated the problem of substandard and falsified medicines, as demonstrated by the rapid appearance of falsified chloroquine preparations after chloroquine and hydroxychloroquine had been “hyped” as potential therapies for COVID-19.5 The key steps to solve the problem of substandard and falsified medicines include prevention of the entry of such product in the health supply chain, quick and widespread detection of those products which still found their way into the supply chain, and adequate responses to remove them from circulation and prevent recurrence.

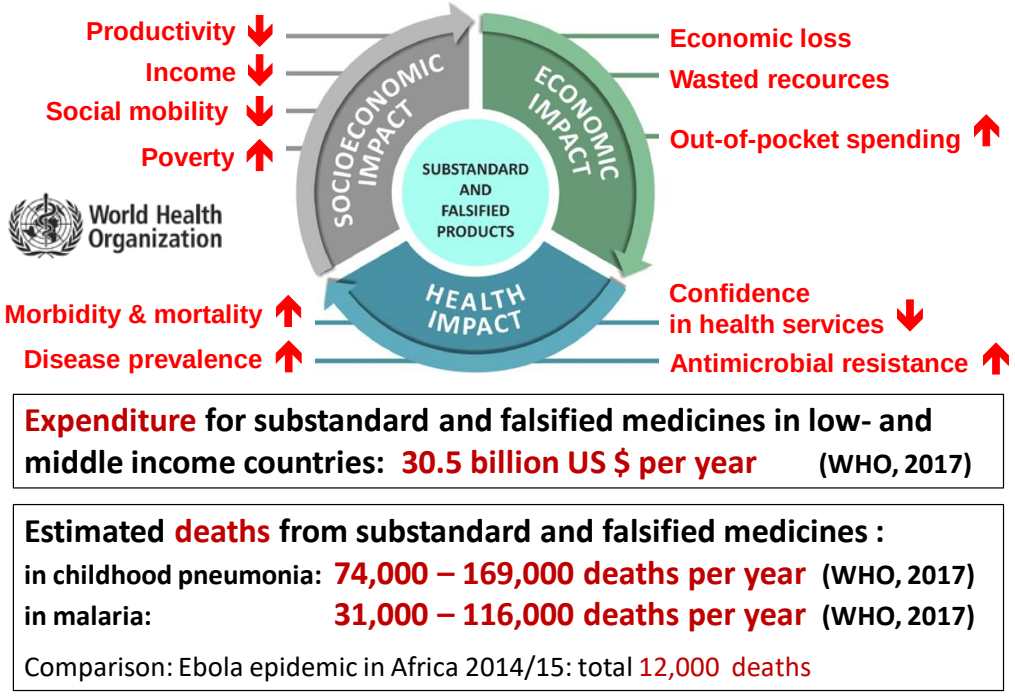

Figure 2: Impact of substandard and falsified medical products. Modified from [6].

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4.4 Drug quality control in Kenya: decadal results from two laboratories (2011-2020)

Kennedy Abuga[1], Stanley Ndwigah[1], Beatrice Amugune[1], Dennis Ongarora[1], Peter Njogu[1], Alex Okaru[1], Stephen Kigera[2], Mildred Wanyama[2], Wycliffe Nandama[2], Isaac Kibwage[1,3]

[1] Faculty of Health Sciences, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya, e-mail: koabuga@uonbi.ac.ke,

[2] Mission for Essential Drugs and Supplies, P.O. Box 78040 – 00507, Viwandani, Nairobi

[3] Egerton University, P.O. Box 536-20115, Egerton-Njoro, Kenya

This is a three-pentad report of quality control results from the Drug Analysis and Research Unit (DARU), University of Nairobi laboratory and Mission for Essential Drugs and Supplies (MEDS) laboratory covering the period 2011-2020. Two DARU reports for 2011-2015 [1] and 2016-2020 as well as one for MEDS covering 2013-2017 [2] are presented. The laboratories received samples from pharmaceutical manufacturers and importers, regulatory authorities, non-governmental organizations, donor-funded programmes, government agencies and hospitals domiciled in Kenya and other sub-Saharan Africa countries in the context of routine quality control. The samples comprised of medicines for human use, veterinary drugs and non-drugs such as excipients, solvents and environmental monitoring swabs. The sample profiles, failure rates and non-compliant drug classes are summarized in Table 2.

Table 2: Quality control results for samples analyzed in DARU and MEDS laboratories.

	DARU 2011 – 2015	**DARU 2016 - 2020**	**MEDS LABORATORY 2013 – 2017**
Samples:			
Total	1972	326	6853
Local	21.5%	32.5%	31.9%
Imported	78.2%	65.7%	67.9%
Unknown	0.3%	1.8%	0.1%
Human	87.6%	88.0%	92.8%
Veterinary	12.4%	10.1%	1.4%
Others	<0.1%	1.8%	5.8%
Failure rates:			
Overall	4.5%	1.8%	5.1%
Local	2.5%	0.6%	1.2%
Imported	2.0%	0.9%	3.8%
Undeclared	-	0.3%	<0.1%
Drug classes failed	Uterotonics (37.5%), hemostatics (33%), anthelmintics (17%), anticancers (10.5%)	Anti-ulcers, hypoglycemics, Opioids, herbals (tadalafil adulterated) - 1 sample each Antiseptics – 2 samples	Antimyasthenics (50.0%), antiseptics (24.7%), anthelminthics (22.0%), thyroid/antithyroid (20.0%), nutrient mixtures (18.5%), uricosurics (12.5%), Waters (11.6%), mixed anti-infectives (11.1%), hemostatics (10.0%), nootropics - 10.0%

Majority of the samples received were imports showing the low local manufacturing capacity of pharmaceuticals. The MEDS laboratory had a higher sample load and throughput relative to DARU due to enhanced capacity for equipment and manpower as well as analysis of internal samples in support of the supply chain functions of MEDS. Additionally, its WHO pre-qualification status gains appeal with international clients. Furthermore, the laboratory had higher non-drug samples mainly received from manufacturers for shop floor environment monitoring, water quality and cleaning validation. The two laboratories faced similar challenges with respect to shortage of equipment, staffing, reference standards and validated methods of analysis.

The results obtained demonstrate that the quality of medicines processed in the laboratories has improved over time. However, the failure rates for anti-infectives are of concern due to the risk of antimicrobial resistance and adverse patient outcomes. The MEDS data revealed 23 substandard and falsified medicines devoid of active ingredients. There is need to strengthen regulatory stringency and mainstream post market surveillance and pharmacovigilance systems to ensure quality assured medicines in circulation.

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4.5 Ensuring Quality of Medicines: Experience from Tanzania

Kissa Watson Mwamwitwa[1,2], Adam M. Fimbo[2], Danstan Hipolite[2], Eliangiringa Kaale[1]

[1] School of Pharmacy, the Muhimbili University of Health and Allied Sciences, P.O. Box 65545, 11103, Upanga West, Dar Es Salaam, Tanzania, e-mail: ki313ssa@yahoo.com

[2] Tanzania Medicines and Medical Devices Authority, P. O. Box 77150, Dar es Salaam, Tanzania

The problem of falsified and substandard medicines is a global issue affecting many countries including Sub-Saharan Africa [1,2]. This made different Medicines Regulatory Agencies to set medicines quality assurance systems to embark on the problem. Thus, Tanzania Medicines and Medical Devices Authority (TMDA) is utilizing two approaches to ascertain the quality of medicinal products circulating on the market. The first approach is a routine quality assurance monitoring of the medicines which is an approach to ascertain the quality of medicinal products by conducting routine sampling at the port of entries (POEs) and random sampling of

suspicious products through inspection and laboratory testing. The second approach is a structured Post Marketing Surveillance (PMS), which is a systematic quality assurance to monitor the quality of registered medicines circulating on Tanzania market after they have been subjected to and passed the pre-registration assessment processes.

Results of quality monitoring of medicines by using the routine quality assurance since 2005 to 2021 indicated that a total of 325 were identified as falsified (96) or substandard (229). Under the structured PMS, different medicines were monitored for quality. Results indicated that all anti-hypetensive sampled medicines (32) atenolol, (7) nifedipine, (27) captopril and (24) furosemide, which were subjected to the test, passed quality parameters with exception of only 14.3% (1/7) of nifedipine which failed assay. Results were ranged from 69.4 - 79.5% (Limit 90% - 110%) [3]. The failure in assay could be a result of degradation of the active ingredient attributed by light sensitivity nature of the active ingredient [4, 5], less light protection capacity of the primary container or fault in manufacturing process of the product.

A total of 777 anti-TB samples were collected from targeted sampling points between January 2012 and December 2018. A total of 31.8% (247/777) were sampled from distribution outlets and the remaining 68.2% (530/777) were collected from POEs. All samples passed screening and confirmatory testing [6].

For antiretroviral (ARVs) medicines, a total of 2,630 samples were collected between 2012 and 2018 from different location. Samples from POEs were 83.7% (2,200/2,630) and medicine distribution outlets were 16.3% (430/2,630). The results indicated that 3% (3/100) failed confirmatory test. The failed samples were of Fixed Dose Combination (FDC) of stavudine/lamivudine/nevirapine in which 2% (2/100) failed disintegration test and assay test 1% (1/100), having low content of stavudine (86.6%) of the specified amount (limit 90% -110%) [7].

Regulatory actions taken included the recall from the market of all failed batches and manufacturer was directed to conduct thorough investigation whilst suspended the importation.

In conclusion, the quality assurance survey has indicated that there is an improved quality of medicines in Tanzania. However, the presence of some few substandard and falsified medicines signifies the need for continuous monitoring of the quality of medicines post registration.

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5 Drug Procurement, Storage and Distribution

5.1 *Introduction to Drug Procurement, Storage and Distribution (Logistics)*

Chukwuemeka Paul Adiukwu

School of Pharmacy, Faculty of Health Sciences, Block 244H/122, Plot 4775 Notwane Rd., University of Botswana, e-mail: adiukwup@ub.ac.bw

Logistics required in the management of health care or drug products is aimed at ensuring availability and appropriate use. Such logistics are provided by a management support system (MSS) which is the support framework for a functional drug management cycle (DMC).

Figure 3: Drug Management Cycle (DMC)

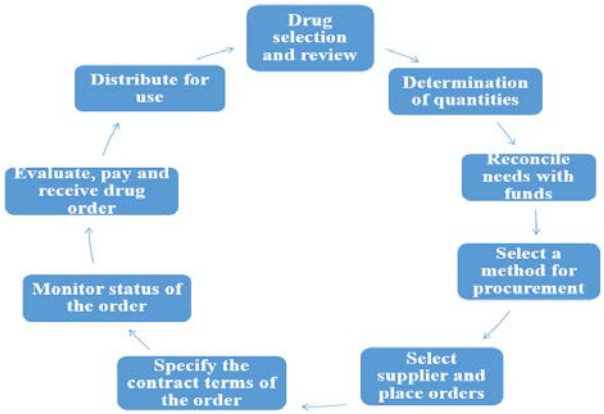

Figure 4: Typical Procurement cycle

DMC is a cycle that provides the practical steps required in the management of drug products as inventory. A functional DMC requires an efficient operation of the various components (Figure 3): drug selection, ordering, procurement, storage, distribution and use. MSS guarantees that quality essential drug products are available at affordable price. By providing necessary logistics for financial, information and personnel management, as well as, organizational support it undertakes the oversight functions in drug selection, ordering and procurement; storage; distribution; and analysis and control of usage.

Selection, ordering and procurement: Basically, selection generates suitable list of cost-effective essential products that can be procured for timely and rational use. Because acquiring all the drug products in commerce is not feasible, organisations require an essential list of drug products which are carefully selected. A carefully selected list is a product of rational use informed by the institutional treatment guidelines. Therefore, the right quantities are determined by employing evidence obtained from the analysis and control of usage.

Acquiring the selected items require guided steps for ordering and procurement. Drug ordering and procurement procedure may slightly vary depending on the organisation or country. However, the components (as shown in Figure 4) are essentially the same.

Storage: Storage is the act of stowing or retaining any item temporarily or permanently as maybe suitable. Drug products are commonly procured in bulk to avoid stock out. By observing good storage practices (GSP), quality of the products is maintained during storage [1]. It should be noted that good storage extends through the shelf-life to waste disposal of the product. As such, it requires the right physical facility, space and personnel.

Distribution: This is the movement of the drug products from a central storage facility, usually the manufacturer or wholesaler, down the supply chain network to different locations or/and point-of-use locations. It is a routine logistic activity in response to placed orders. The activity is considered a requisition or pull system when the quantity to be supplied is determined by persons placing the order. It is allocation or push system if the quantity is determined by persons filling the order [2]. Whichever case this may be, it is important to monitor the operational and human management.

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5.2 Algorithm and Role of Storage in Drug Management Cycle

Chukwuemeka Paul Adiukwu

School of Pharmacy, Faculty of Health Sciences, Block 244H/122, Plot 4775 Notwane Rd., University of Botswana, e-mail: adiukwup@ub.ac.bw

Stock outs of health care products especially, drug products have remained endemic to developing economies. At the fore front of possible collateral damage, if the present status quo remains, are the low- and mid-income countries. In recent time, improving access to health care products has attracted concerted attention from major stakeholders. The Sustainable Development Goals, 2030 agenda has generated required need to adjust activities at all levels of the World Health Organisation in addressing access to health care products [1]. Therefore, it is imperative to critically review the contemporary good storage, vis-à-vis the process and role of various components of the Drug Management Cycle (DMC) in mitigating the effects of stock out.

Proper management of drug products can optimize efficiency in storage activities, minimize costs to storage, reduce cost of product and improve accessibility. Irrespective of the type of storage systems (shelving, racking, stacking or special storage systems) and adopted storage method (self, warehousing or subcontracting), the ultimate goal of a good inventory

management is to prevent product loss and spoilage, as well as, ensure tracking and inventory value protection. Hence, good storage is a major component in ensuring accessibility to drug products, as well as, mitigate the effects of stock out.

Good storage is knowing what, where and how to store for timely and safe use. It abhors damages or losses and ensures rational utilization borne out of the application of efficient DMC. The procedure for good storage can essentially be guided by two factors: (i) Basic requirements for good storage which includes the physical facility, store space and security for facility and product; and (ii), activities and practices which include good storage practices and logistics.

The need for logistics addresses the requirement of an effective DMC through the components which include drug selection, ordering, procurement, storage, distribution and use. Fundamentally, operational DMC provides the required drug product information. Failure in any of the components ultimately leads to lack of access and increase in wastages [2].

Despite an efficient DMC to support good storage, developing countries particularly in Sub-Saharan Africa, still grabbles for realistic solutions to stock outs. This is complicated by the increasing health care waste products emanating from expired drugs. Evidences have shown that good quality active pharmaceutical ingredients can be recovered from expired drug products [3,4]. This can help to address stock outs. As such, emerging role for good storage of expired drugs is required. In fact, the adequacy of the recycled active pharmaceutical ingredients will be sufficiently enabled with good storage which will prevent accelerated product deterioration during storage.

Keywords: Drugs, good storage, emerging, expired, stock outs.

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6 Safe Disposal of Expired Drugs

6.1 Introduction to Safe Disposal to Expired Drugs

Matiwos Ensermu[1], Dawit Teshome Gebregeorgise[2]

[1] Department of Logistics and Supply Chain Management, School of Commerce, Addis Ababa University, e-mail: matiwos.ensermu@aau.edu.et

[2] School of Pharmacy, College of Health Sciences, Addis Ababa University

Unused or expired medicines should be disposed of properly to avoid health and environmental harm. Key stakeholders in the pharmaceutical supply chain such as government agencies (e.g. Quality Control Authorities), Hospitals, Clinics, suppliers, drug manufacturers, importers, drug distributors pharmacy chains, retailers, research organizations, and Customers can take various preventive measures. One of these is applying sustainable public procurement practice which is crucial to achieve value for money on a whole life basis for the benefit of society and the economy (Indiana University, 2018), while minimizing damage to the environment. The pharmaceutical procurement process should also take into account the entire lifecycle of the product or service using a Life-Cycle Costing Approach: the life-cycle costing is used to measure and compare costs including those attributed to environmental externalities: Investment, operation, maintenance and, disposal costs.

In the literatures, several safe and environmentally friendly disposal methods have been documented. Drug take program is one of these [1]. It is a widely used safe disposal method particularly for medicines that expire in patients' households. In situation where there is no drug take back program, users may dispose medicines with negligible human and eco-toxicological risk by flushing down the toilet [2]. Drug take-back events should be supported by law enforcement to make this option productive [3].

Returning expired medicines such as antineoplastic to manufacturers is also another safe disposal practice. Because of the ignitability, corrosivity, reactivity and toxic characteristics of some products, they should be returned to manufacturers. Some medicines can also be buried into a land disposal site with or without prior treatment or preparation. Modern landfills that are well-engineered and managed facilities for the disposal of solid waste protect the environment from contaminants. Some medicines can be immobilized by encapsulation or inertization.

Incinerating at a temperature of 850°C to 2000°C is another way of disposing of medicines safely. To protect human health, appropriate equipment to control atmospheric pollutants must be used, since the legal limits for pollutant concentrations were strongly surpassed (226 times higher than the limit for Hg), with risks for patients and workers of the hospital and exposed population [4].

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6.2 Disposal of Expired Drugs

Lucie Moeller

Department “Centre for Environmental Biotechnology”, Helmholtz Centre for Environmental Research GmbH (UFZ), Permoserstr. 15, 04318 Leipzig, Germany, e-mail: lucie.moeller@ufz.de

The production and sale of pharmaceuticals is steadily increasing from year to year [1]. Accordingly, the amount of pharmaceutical waste is also growing rapidly. However, the presence of some types of pharmaceutically active compounds in the environment in increased concentrations can cause disturbances of sensitive ecosystems. Therefore, responsible handling with pharmaceutical waste such as expired and unwanted drugs is needed.

The actors involved with pharmaceutical waste generation and management include doctors and hospitals. Hoarding and non-adherence to treatment contribute to waste. Therefore, health professionals have to inform patients about the importance of completing prescribed courses of treatment, and discourage them from hoarding medicines after their expiry date. Moreover, the physicians should not prescribe more than the required quantity of medicines, e.g. by prescribing minimal quantity in spite of a new therapy when it is not clear if the drug is in fact suitable for the patient. Further actors are also the patients themselves. There are several studies to the disposals of unwanted medicines by consumers in countries of Sub-Saharan Africa (e.g. [2], [3], [4]). In general, the factors contributing to non-usage and disposal are: change of prescription, adverse effects of the drug, unclear instruction, resolution of condition or clinical symptoms, expiry date [2,3]. The major discarding practices for medications were stated to be disposal into domestic trashes and pit latrines/toilets [2,3,4]. Only a minority was

aware of having the possibility to return the unwanted medicines to pharmacy or to a healthcare provider, who are also one of the actors dealing with pharmaceutical waste.

According to the “Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies” of WHO [5], there are seven possible disposal methods for pharmaceuticals: (1) return to donor or manufacturer (whereas the Basel convention, Bamako convention as well as the Stockholm convention are to be considered); (2) incineration (preferably at high temperatures in excess of 1,200 °C; if medium temperatures of 850 °C are applied, two-chamber incinerators have to be used); (3) immobilization (in form of waste encapsulation in a solid block within a plastic or steel drum that is to be placed at the base of a landfill, or in form of inertization of unpacked pharmaceuticals that are ground and mixed with water, cement and lime and decanted into the municipal solid waste in a landfill); (4) landfill (highly engineered sanitary landfill consisting of an evacuated pit isolated form watercourses and above the water table is the method of choice for pharmaceuticals preferable after immobilization; engineered landfill containing features for protection of aquifer form loss of chemicals may be also used as the second best choice after immobilization; open uncontrolled non-engineered dump has to be used as the very last option and the waste – if not immobilized – has to be covered immediately with municipal waste to prevent scavenging); (5) sewer (only for diluted liquids in small quantities); (6) burning in open containers (may be used as a last resort because toxic pollutants may be released into the air, usable only for packaging, paper and cardboard); and (7) chemical decomposition (according to the manufacturer’s recommendations, followed by landfill; only applicable for small quantities).

Alnahas et al. [1] stated, that “A waste of pharmaceuticals is, to some extent, a waste of ethics“. Actually, less than 2% of drugs consumed in Africa are produced on the continent which leads to preventable deaths because patients do not have access to locally produced medicines and many cannot afford to buy the imported ones [6]. One possibility would be the shelf life extension as established by U.S. Department of Defence and the USFDA for the military stocks of the USA. According to their experiments, approximately 90 % of 3,000 batches of medications tested were valid for use after the expiry date [1]. However, it has to be mentioned that the drugs in military stocks are stored under ideal conditions so that these results cannot be easily transferred to expired drugs that were collected from households. For this case, innovative stability tests have to be developed and offered by pharmaceutical manufacturers.

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6.3 The Costs Resulting from Pharmaceuticals Waste

Matiwos Ensermu[1], Dawit Teshome Gebregeorgise[2]

[1] Department of Logistics and Supply Chain Management, School of Commerce, College of Business and Economics, Addis Ababa University, Addis Ababa, Ethiopia, e-mail: matiwos.ensermu@aau.edu.et
[2] Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Supply Chain Management in the pharmaceutical industry follows the same horizontal and vertical structure of pharmaceutical value chain governance. The key stakeholders in this Pharmaceutical supply chain include: Multiple government agencies (e.g. Quality Control Authorities), Hospitals, Clinics, suppliers, drug manufacturers, importers, drug distributors, pharmacy chains, retailers, research organizations, and customers. Sustainable Procurement is a process whereby organizations meet their needs for goods, services, works and utilities in a way that achieves value for money on a whole life basis for the benefit of society and the economy while minimizing damage to the environment [1]. Pharmaceutical procurement process should also take into account the entire lifecycle of the product or service using a Life-Cycle Costing Approach. The life-cycle costing is used to measure and compare costs including those attributed to environmental externalities: Investment, operation, maintenance and, disposal costs. Keeping unused medicines at home, disposal of unused medicine by throwing in to trash, disposal of medicines by flushing them down the toilet and burning unused medicines are the common methods observed for pharmaceutical waste disposal in Ethiopia, Kenya, Sudan and Uganda [2]. Furthermore, factors contributing to medicines wastage in public health facilities of South West Shoa Zone, Oromia Regional State, revealed that supplier-related factors such as: supplying near expiry products and applying push system in some cases and internal factors such as: weak inventory management, lack of sufficient

human resources for pharmaceutical services, lack of medicines' transfer policy, shortage of storage spaces and poor communications across various units in other cases, were identified to be significant drivers of wastages in Ethiopian Hospital [3]. Overtime, countries' expenditure on and cost of medicines has been growing. The objective of this study was to estimate the direct costs resulting from pharmaceuticals waste in a case hospital with a quantitative approach. The value of medicines purchased and expired in 2021/22 fiscal year were accessed using the data abstraction forms from the case observation of Tikur Anbessa Specialized Hospital and Ethiopian Pharmaceutical Supply Agency (EPSA), in Ethiopia. The results of the study showed, Tikur Anbessa Specialized Hospital purchased health commodities (i.e. pharmaceuticals, medical equipment and lab reagents and medical Supplies) worth of Ethiopian Birr (ETB) 160,087,976.3 (~ USD 3,078,614.9) in 2021/22 [4]. Of these, health commodities worth of ETB 3,844,050.62 (~ USD 73,924.05) wasted at stores before being distributed to dispensaries in the hospitals. Most of these expired products were pharmaceuticals (90.86%), medical equipment and lab reagents (6.65%) and medical supplies (2.48%). Anti-cancer, COVID-19 Vaccines and insulin that are vital items are among the top ten expired medicines by value. In similar case observation at EPSA, from the annual procurement of ETB 17,011,435,811.59 (~ USD 340,228,716.2318); 2.32% was pharmaceutical waste, which is, equivalent to ETB 394,665,311 (~ USD 7,983,306) [5]. If the wastage was accounted in dispensaries and medical wards, the direct medical cost would have been higher than reported ones. Based on the results of this study, health commodities wastage including pharmaceuticals is growing public health, environmental and financial concern. However, the real magnitude of the problem is often under reported. More evidence needs to be generated and appropriate design should be in place to minimize the direct and indirect medical and nom medical cost of pharmaceuticals and other health commodities wastage.

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6.4 Expired drugs and the ecosystem – reflections from Botswana

Julius R Atlhopheng, Pulane Koosaletse-Mswela, Piet Kenabatho, Kgabisang Puni Gaboutloeloe

University of Botswana, Department of Environmental Science, e-mail: ATLHOPHE@UB.AC.BW

Introduction

The use of drugs leads to waste which accumulates on the ecosystem [1] resulting in ecological, economic, social and ethical challenges. The realities of expired pharmaceutical drugs, over time, load the environment with tonnes per year of expired/excreta of drugs. The impact of these on the planet sustainability [2-4] and ecological integrity are spatially variable. The carrying and or assimilative capacity of the environment, is not always known, and in some instances even the concentration levels in different mediums of soils, wastewater, as they relate to sanitation and health standards. There is need to document the level of expired drugs in ecosystem, as a duty to healthy living and ecosystem integrity [4]. This study has thus prioritised the following objectives: i) to assess the compendium of pharmaceutical drugs in soil and wastewater systems; ii) to evaluate the risks associated with handling, safety and microbial biodiversity impacts and their economic costs; iii) to assess the legislative/policy environment on expired drugs in terms of reusability, efficiency and sustainability assessments, and standards for a secure future.

Key considerations for ecosystem safety

The study by Mahara et al. [5] showed over 60% concern on unsafe disposal of expired drugs. Population increases and increased disease burden [4] highlight the persistent threat of pharmaceutical wastes. The world, as it recovers from covid19, needs to build-back better, after intensified drug usage. This study espouses the waste-to-wealth strategy on expired drugs, the enhancement of biosafety levels in the soil and wastewater systems, ensuring intergenerational equity to avoid passing on pollution and waste as inheritance or legacy for the future. The promulgated solutions are thus in having sound environmental management plans, which assess the impacts of expired drugs. The initiatives include integrated resource planning by industries, producers and users; pollution and waste impact matrices; understanding the mediums of deposition in relation to biogeochemical cycles/processes in the soil-air-water continuum; and the effect on food safety and security as there may be bioaccumulation and biomagnifications. Secondly, the human settlements tend to be vulnerable to contaminants and unsafe levels. The solutions include – a) Legislation/policy on environmental safeguards relating to expired drugs; b) more awareness and audits on settlements sustainability with regard to expired drugs (social, economic, environmental); c) imbibe just transition opportunities through strategic green growth, efficiencies; standards; prioritise public education on potency of expired drugs, as there is low public awareness e.g. on expiry date vs. safe use/stability testing; drug waste logistics. There is need to adopt 4IR

digital initiatives (e.g. bar coding of drugs in terms of their use levels) to enhance data, services and value chains. The final dimension on solutions for expired drugs relate to risks i.e. documenting the risks and impact interventions for safety of society. With expired drugs, there is need to have: a) baseline data on expired drugs, whose categories may include the WHO indispensable medications, antibiotics, the risks of garbage & sewer disposal methods vs other more strategic methods; b) to instil Monitoring & Evaluation protocols – on re-use, recycle e.g. active pharmaceutical ingredients (APIs) possible re-use in generic medicine developments [6,7]; secure handling of heavy metals as they are contained in e.g. in supplements, as these need higher incineration temperatures, to ensure their safety. As expired drugs increase, there is need for (c) more sustainable design parameters of storage/disposal sites (with more Life Cycle Analysis approaches, in line with circular economy). The EU, 2022 report on covid19 impacts on environment [8], and Desai [9] relate environmental loading of pharmaceutical wastes, arising from the pandemic.

Conclusions

New planning needs to highlight the true costs of expired drugs to the economy – usage cost per age group e.g. per person per year; usage per patient; food substances exposure to food e.g. for dairy, the milk shelf life for cows exposed to pharmaceutical contaminants. Desai et al. [9] indicate the ubiquity of active pharmaceutical ingredients across medium types (sewage, surface, groundwater, soil, air, biota). It is possible to implement solutions such as drug take-back programme, and drug donation- to avoid more wastage. The environmental loading and monitoring mechanisms, need prioritised capacity building, and the use of 4IR/ICTs for enhanced services, products and data transformations. Data needs to be interoperable across different sectors, in as much as logistics, storage and expiry details, are critical for e-records. Sharing of data across sectors is critical, thus more data approaches are critical.

Cross-sectoral approaches are critical in expired drugs tracking as medicines disposed of in sinks/flushed down end in wastewater systems, whereas those dumped into bins end up in landfills, causing adverse impacts in the soil-water-continuum. Thus, better policies, and their integration remain critical in solving most challenges.

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7 Wastewater Treatment to Remove Toxic and Environmentally Problematic Drug Substances and Metabolites

7.1 Introduction to the topic

Roland A. Müller

Department "Centre for Environmental Biotechnology", Helmholtz Centre for Environmental Research GmbH (UFZ), Permoserstr. 15, 04318 Leipzig, Germany, e-mail: roland.mueller@ufz.de

The challenges surrounding sustainable water management and sanitation today expand well beyond the removal of common pollutants such as nitrogen and phosphorus from wastewater. The release of micropollutants and pathogenic organisms to the environment can place humans at risk via direct contact with or consumption of contaminated food and/or drinking water. This problem is particularly pertinent in developing countries, where even basic sanitation is often lacking. The continuous release of complex mixtures of thousands of micropollutants to the environment results in measurable toxic effects. Current wastewater technologies, regardless of type or size, have not been specifically designed to remove this complex mixture of chemicals. Nature-based technologies such as treatment wetlands clean water using natural processes. They are energy-efficient, robust, and inexpensive to operate. They can also be built with local materials and in a modular approach according to population dynamics and future needs. One essential option for future activities are integrative methods from eco-toxicology, analytical chemistry and engineering to create new technologies that are designed to remove micropollutants, pathogens, and eco-toxicological effects from wastewater and thus, helps to reduce contamination loads into the rivers. Eco-toxicity should be introduced as an important component of wastewater treatment, in both education and in practice. Decision support will educate decision makers and stakeholders in developing countries about the environmental risks of wastewater and help them identify investment priorities for safeguarding water resources at a local level.

7.2 Occurrence and removal of pharmaceutical residues in water: A case study of the Lake Victoria basin-Kenya

Faith Kandie[1], Kenneth K'Oreje[2,3], Martin Krauss[4], D. Kristof D.[3], Baldwyn Torto[5], Werner Brack[4,6]

[1] Biological Sciences, Moi University, e-mail: kandiefaith@gmail.com

[2] Environmental Organic Chemistry and Technology (EnVOC) Ghent University, Coupure Links 653 9000 Ghent, Belgium;

[3] Water Resources Authority (WRA), P.O. Box 45250 00100, Ngong Road, Nairobi – Kenya;

[4] Helmholtz Centre for Environmental Research (UFZ), Permoserstr. 15, 04318 Leipzig, Germany;

[5] International Centre of Insect Physiology and Ecology (Icipe), P.O. Box 30772-00100 Nairobi, Kenya;

[6] Faculty of Biological Sciences, Goethe University Frankfurt, Max-von-Laue-Str. 9, 60438 Frankfurt, Germany.

In the recent years, global concerns have increased on the environmental occurrence of Pharmaceutically Active Compounds (PhACs) due to their pronounced ecotoxicological risk. Several studies have shown their presence in different environmental matrices including water, sediments and biota. Whereas the occurrence of these compounds has been widely studied in the western world, few studies have been done in Africa. Additionally, the fate of PhACs during wastewater treatment by stabilization ponds and trickling filters commonly used in low-income countries, is not well known. To narrow this knowledge gap, this study investigated the occurrence of PhACs in water, snail tissues and sediments in 48 surface water systems and their removal in four selected wastewater treatment plants (WWTPs) within the Lake Victoria Basin, Kenya. Water samples from surface water were directly injected into the Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) for chemical analysis while wastewater samples were first processed using solid-phase extraction before analysis. Extraction of chemicals in snail tissues was done using QuEChERS (quick, easy, cheap, effective, rugged and safe) method while pressurized liquid extraction was applied to sediment samples prior to chemical analysis.

Out of the total 157 target compounds, 25 were detected in water, 5 in snails and 18 in sediments from surface water system samples. For water samples, detection frequencies ranged from 2% to 90% (anti-allergic drug diphenhydramine). This frequent detection could be attributed to the availability of several over the counter drugs that contain diphenhydramine as one of the main active ingredients [1]. Individual compound concentrations varied from 0.001 to 24 µg L^{-1} (acetyl-sulfamethoxazole). Acetyl-sulfamethoxazole is a transformation product of sulfamethoxazole, an antibiotic used to treat various bacterial infections in both humans and livestock [2,3]. In snails, highest detection frequencies were reported for the psychotic drug temazepam (98%) and compound concentrations were up to 137 ng/g ww (efavirenz). For sediments, efavirenz was most frequently detected (56%) and also in high concentrations (up to 29 ng/g OC). This frequent detection and high concentrations could be attributed to the high

HIV/AIDS prevalence (16.3%) and the access to antiretroviral therapy (ART) with a coverage of 90% [4] in the region. Efavirenz is a non-nucleoside reverse transcriptase inhibitor used in combination with other medications as antiretroviral treatment for HIV/AIDS [5]. For wastewater samples, a total of 23 out of 39 target pharmaceuticals were found with antibiotics being the frequently detected and analgesic/anti-inflammatory drugs reporting highest concentrations (up to 630 µg L^{-1}, paracetamol). Overall, more than two thirds of the PhACs were removed by better than 70% after anaerobic and primary facultative ponds while maturation ponds played minimal (polishing) role in the removal of PhACs in wastewater stabilization ponds. Compounds such as carbamazepine and nevirapine had low removal efficiencies (average 44% and 52% respectively) which is similar to other systems e.g., activated sludge [6,7].

This study builds on previous research on multi-compartment analysis of PhACs in surface and wastewater systems in Kenya and provides comprehensive data on PhACs compounds in a rather data limited region. Results show that water systems are contaminated with PhACs which might pose a risk to exposed organisms, however WWTPs are effective in removal of some compounds while some remain recalcitrant. Further research should focus on the dynamics in the removal of individual compounds during treatment.

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7.3 Perspectives of decentralized waste water treatment systems for transient and developing countries

Roland A. Müller, Nadine A. Sossalla and Manfred van Afferden

Department "Centre for Environmental Biotechnology", Helmholtz Centre for Environmental Research GmbH (UFZ), Permoserstr. 15, 04318 Leipzig, Germany, e-mail: roland.mueller@ufz.de

Decentralized wastewater systems collect, treat, and reuse or dispose of wastewater at or near its point of generation. Decentralized wastewater treatment systems are defined as follows: "Domestic wastewater treatment plants for small residential groups with a design capacity below 5.000 Population Equivalent". A centralized management of decentralized clusters of technologies often is an adequate operation and management concept.

Conventional centralized wastewater treatment plants are one of the biggest sources of micropollutant release to the environment. The original aim of wastewater treatment was to minimize the nutrient burden released to the environment, which was known to be the cause of extreme eutrophication of surface waters. In recent decades, tertiary treatment steps have been added to existing wastewater treatment plants for enhanced nutrient removal, pathogen removal, and more recently, removal of micropollutants. Tertiary wastewater treatment generally involves physical processes (e.g., activated carbon, sand filtration) or chemical processes (e.g., ozonation and advanced oxidation). In some countries, chlorination used to ensure disinfection. Advanced wastewater treatment technologies such as ozonation can eliminate pathogens and some micropollutants from wastewater, but can also generate potentially harmful substances (e.g., disinfection byproducts or transformation products) that in the end, may pose a greater environmental risk than the original compounds of concern [1].

An alternative to conventional wastewater treatment technologies are decentralized and nature-based technologies, which are in the focus of the presentation. Nature-based technologies clean water via natural processes as opposed to traditional methods, which rely on external chemical or mechanical inputs. Nature-based technologies include treatment wetlands, green roofs, rain gardens, and vegetated swales, among many others. These technologies focus on retention and treatment of water on a local scale. A special aspect of nature-based technologies is that they can be integrated into the local environment and are intended to provide many additional ecosystem services beyond water quality improvement including, but not limited to, rainwater retention, flood alleviation, increased biodiversity,

reduced stress on local water resources, lower energy demands for buildings, increased food production, and creation of local water cycles.

New research is increasingly focusing on the behaviour of effects to the environment caused by micropollutants. The release of these anthropogenic chemicals into the environment creates a complex mixture of chemicals that can cause measurable adverse biological effects. While recent studies indicate the ability of treatment wetlands to remove micropollutants, major questions regarding the removal efficacy of biological effects, the most efficient design aspects (aerated vs. non-aerated; planted vs. non-planted; single-stage vs. two-stage), the resiliency of a treatment wetland, and the potential for optimization are still unsure. The existing knowledge gaps have to be addressed and the understanding of treatment technologies as well as the potential of treatment technologies to reduce micropollutants and biological effects have to be improved.

Seven treatment wetlands and a municipal wastewater treatment plant were examined over the course of an entire year, to identify the most effective design of the treatment plants in terms of biological effect removal [2]. Intensified wetlands showed higher annual removal efficacy (41 - >99%) than the non-aerated (conventional) horizontal flow wetland (24 – 78%) for investigated micropollutants and biological effects. Removal efficacy for carbamazepine, which is considered to be resistant to aerobic biodegradation, was observed to be higher in the nonaerated horizontal flow treatment wetland than in the intensified wetlands (24 %, 0 – 3 %, respectively). Benzotriazole, diclofenac, activation of aryl hydrocarbon receptor, activation of peroxisome proliferator-activated receptor gamma, and oxidative stress response were removed to a greater extend through the intensified treatment wetlands than by the municipal wastewater treatment plant. Also, for the first time, the effluent qualities of the treatment wetlands were compared with recently proposed effect-based trigger (EBT) values for surface water. The effluent bioanalytical equivalent concentrations for all intensified treatment wetlands and the municipal wastewater treatment plant were close to or even below the surface water EBTs, except for estrogenicity. This indicates the great benefit of using nature-based solutions for water treatment because the treated effluent would not impose a negative ecological effect on a receiving water. Aeration and therefore an elevated oxidation reduction potential was identified as a key environmental condition for increased removal of micropollutants and biological effects. In particular, the two-stage system (aerated vertical flow constructed wetland followed by an unsaturated vertical flow sand filter) achieved the highest removal efficacies for conventional parameters (66 to >99%), micropollutants (94 – 99%, except carbamazepine: 3%) and biological effects (91 – 99%). But also, the less cost-intensive one-stage treatment wetlands (aerated horizontal flow and aerated vertical flow) achieved high quality effluents for the observed parameters.

With different aeration strategies, aerobic and anaerobic zones were created in an aerated horizontal flow treatment wetland. The sharp increase of the oxidation reduction potential resulted in a higher removal for the moderately biodegradable micropollutants benzotriazole (77– 97 %), diclofenac (50 – 94 %) and carbamazepine (-43 – 37 %). But, the removal efficacy of biological effects decreased with the enlargement of the non-aerated zone in the treatment wetland. Nevertheless, the combination of aerated and non-aerated zones can reduce moderate and recalcitrant micropollutants. The advantage of high removal efficacy for micropollutants and biological effects through aeration comes with the susceptibility to technical disturbances such as a power failure or an air pump failure. A simulated aeration interruption of six days resulted in a poorer water quality (comparable to that of a conventional non-aerated horizontal flow treatment wetland). After switching the aeration back on, the investigated system recovered within a few days for most of the conventional wastewater parameters (8 – 22 d) and micropollutants (3 – 22 d). Results showed that removal of biological effects are negatively affected for a longer period of time (>22 d) than what was indicated by classical parameters or micropollutants alone. These results mark the importance of the use of bioassays for future water quality assessment.

With respect to the removal of biological effects, three treatment wetland designs can be recommended: the two-stage system (aerated vertical flow treatment wetland followed by an unsaturated vertical flow sand filter); and the less cost-intensive one stage systems: aerated horizontal flow treatment wetland and aerated vertical flow treatment wetland. The aerated horizontal flow treatment wetland is also resistant to an aeration interruption of a couple of days and recovers, even if it takes longer than indicated through conventional wastewater parameters and micropollutants [2].

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7.4 Pharmaceuticals in river water: implications on human and ecological health

Oarabile Mogobe, Barbara Ntombi Ngwenya

University of Botswana, Okavango Research Institute, P/Bag 285, Maun, Botswana, e-mail: omogobe@ub.ac.bw

Deterioration of freshwater quality has become a challenge for humanity in the twenty-first century. Unfortunately, aquatic ecosystems are prone to pollution because they act as sinks; receiving, accumulating and transporting numerous chemical contaminants released into the environment [1]. The Anthropocene era has seen a human dominated planet with increasing population, socio-economic prosperity, climate change and disease burden. These activities are exerting enormous pressure and driving the release of pollutants into natural ecosystems. Pollution of freshwaters has been well studied, with scientists establishing the presence and concentrations of several pollutants such as nutrients, heavy metals, organics and pesticides. Pharmaceutical residues have emerged as 'new contaminants of concern' in aquatic environments, posing threat to human and ecological health [2]. However, the occurrence, concentrations and effects of pharmaceutical pollutants are unknown for many rivers of the world, especially African rivers [2, 3]. This paucity of information is a challenge for the effective management of aquatic ecosystems and the protection of human and ecological health. This work attempts to review a few published studies that assessed the status of pharmaceutical pollution in world Rivers, African Rivers and the SADC region. The review revealed that most drug residues occur at higher concentrations in African water bodies compared to observed levels in Europe or USA [4]. The pharmaceuticals frequently detected in relatively high concentrations were analgesics which are easily purchased over the counter in drug and food stores. The other notable drugs reported present in high concentrations were antibiotics, detected in several African water bodies, for example; Ghana, Kenya, Mozambique, South Africa and Nigeria [3, 4, 5]. These papers also reported observed prevalence and persistence of anti-retroviral drugs (ARVs: ritonavir, nevirapine, lamivudine and zidovudine) in African water bodies, not surprising considering their extensive use in the continent. The presence of these pharmaceuticals in river waters could be attributed to the direct discharge of untreated waste into rivers but also this may point to the inefficiency of Waste Water Treatment Plants to remove pharmaceuticals from the effluent. The presence of antibiotics in freshwater ecosystems may exacerbate the development of antimicrobial resistance genes, resulting in increase of drug resistant infections [2, 5] currently responsible for 700 000 deaths every year. Oral contraceptives (oestrogen), when discharged into water bodies caused feminisation of male fish consequently a decline in fish population while exposure to psychiatric drugs caused changes in behaviour of fish, making them more vulnerable to predators [2]. These findings are likely to have a negative impact on ecological biodiversity, nutritional and food security,

especially for riparian communities in developing countries who depend on fish as a major source of livelihood. From the few studies conducted in African rivers, there is evidence of prevalence of ARVs, analgesics and antibiotics in water bodies. However, more data is needed to assist drawing an informed conclusion regarding their prevalence, concentrations and impact on human and ecological health.

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7.5 The potential of constructed wetlands to treat different waste water including emerging components

Uwe Kappelmeyer

Department of Environmental Biotechnology, Helmholtz Centre for Environmental Research GmbH (UFZ), Permoserstr. 15, 04318 Leipzig, Germany, e-mail: uwe.kappelmeyer@ufz.de

Constructed wetlands are near-natural systems for the treatment of various types of wastewater. These systems use the complex interaction of all elements of constructed wetlands. The elements are plants, bacteria and matrix material such as sand or soil. The plants play an aesthetic role, provide oxygen to the subsurface zone, and are the growing surface for preferentially aerobic bacteria. The matrix also provides a surface for preferentially anaerobic bacteria. The used plants are special marsh plants able to live in anaerobic sulfide rich anaerobic water so called helophytes.

The bacterial community living in constructed wetlands shows a very high diversity and span from aerobic bacteria like nitrifying bacteria to strict anaerobic bacteria like sulfate reducing bacteria or methanogenic archaea. This is one of the key features of constructed wetlands to treat a high variety of different chemical components including recalcitrant antibiotics.

The treatment and construction of a demonstration unit installed in Alexandra (a slum in Johannesburg) was highlighted. The transformation involving the nitrogen cycle and removal of selected pharmaceutical components could be shown. For a more closed look into this demonstration units three lab-based systems with similar properties were installed in a greenhouse at the UFZ in Leipzig. These units are used to fish metabolites and investigate the involved microbial community. The biofilm growth on gravel was used to bioaugment a constructed wetland treating ibuprofen and to diminish the lag or adaptation phase.

7.6 Technical and Regulatory Challenges affecting the Disposal of Drugs in Sub-Saharan Africa

Samwel Manyele

Chemical and Process Engineering, University of Dar es Salaam, Tanzania, e-mail: sammanyele@gmail.com

The study on technical and regulatory challenges affecting the disposal of drugs in Sub-Saharan Africa is presented in this paper. The paper highlights on importance of pharmaceutical products and pharmaceuticals and personal-care products in the health framework of each country, and the need for higher stocks to safeguard the populations at health risks. The stocks comprise of one-time use for most of the pharmaceutical products, applied externally or internally, with closer expiry dates, leading to large volumes of waste. Thus, there is a need for proper pharmaceutical waste management and also to categorize it as non-conventional waste due to chances of seepage of active substances into the environment (soil and water bodies). The study shows that although the pharmaceutical products contain active ingredients at very low concentrations (from ng/L to µg/L) ranges, they however pose highly toxic effects. The effluents in the vicinity of the pharmaceutical industries have been reported to contain a wide range of pharmaceutical products.

The study has categorized pharmaceutical waste generators as industry, medical stores, healthcare facilities and research institutions. Moreover, other generators were identified such as households, laboratories and pharmacies, all of which are struggling to treat their waste products, minimizing reagents using alternative non-toxic reagents or synthesis pathways.

The hazards posed by pharmaceutical waste include chemical contents with hazardous characteristics such as ignitability, corrosiveness, toxicity and reactivity, which can affect humans, animals and plants.

The major source of unused expired medicines (UEM) in the waste streams include prescription practices, lifestyle changes, rise of chronic health conditions, availability of generic treatments and changes in clinical practices. Other causes of pharmaceutical products becoming waste were states to be cases of no-effect, lack of adherence, faster recovery of

patients, over stocking, purchasing or prescription error, and poor storage conditions. It was stated however, that there is lack of data in the Sub-Saharan Africa on medicines consumption, amounts of drugs in circulation, amounts of medicine waste and retail pharmaceutical spending.

Estimates were presented from other countries on medicines becoming waste, such as 3-8% in EU, 3-4% in Finland. The data parity was indicated whereby differences in presenting data was highlighted, for example, expressing the UEM as g UEM/capita, percent of household waste in France, or mg APIs/kg of MSW in Florida, USA.

The pharmaceutical waste generation from HCFs was presented using data on measured waste generation rates, and contribution from patients own drugs, admission or assessment units and during patients transfer, pharmacies and stores in HCFs. Packaging waste from pharmaceutical products was also identified as a major source of waste, necessitating application of life cycle assessment for primary and secondary packaging using ISO 14040 and ISO 14044. The paper highlighted that proper selection of packaging can lead to reduction of global warming, reduced primary energy use and reduced respiratory organics in the environment.

The waste management practices presented for all generators included: avoidance, waste minimization (pharmacies and industry), pharmaceutical waste collection and take-back schemes.

Pharmaceutical waste treatment and disposal was discussed at length, covering impacts of improper disposal, disposal methods, the need for secure disposal, challenges of pharmaceutical waste incineration (including heavy metals in the ashes, glass bottles and vials in the ashes, need for further treatment and disposal processes).

The paper presented also the cross-cutting issues related pharmaceutical waste, including challenges (lack of supervisory skills, leachate from landfills), pharmacies operators regarding the pharmaceutical waste as a loss of money, bureaucracy during pharmaceutical waste disposal requiring consensus of many stakeholders, small-scale pharmacies in Sub-Saharan Africa, etc. It was recommended that there is a need for awareness rising by providing information on pharmaceutical waste management, information campaigns, incentives for returning medications and the need for product information and eco-labelling.

Key policy recommendations for improving pharmaceutical waste including: preventing UEM, marketplace and redistribution platforms, customizing the collection of UEM, implementing EPR schemes, putting in place e-Pharmacies and development of drugs take back schemes, etc.

The economic approaches including circular economy and sufficiency economy approaches were also recommended as policy measures. The paper also recommended encouraging the private investment in ESM for pharmaceutical waste management.

7.7 Pharmaceutical waste and environment experience from Botswana

Barbara Ntombi Ngwenya

Okavango Research Institute, Maun, Botswana, e-mail: bnngwenya57@gmail.com

Introduction

The Okavango Delta overs a total surface area of 28,000 km^2 is a Multi-Internationally Designated Area (MIDA) and is recognized nationally and globally for its biodiversity and wildlife. The Delta is characterized by a mosaic of habitats that range from permanent swamps to seasonally flooded swamps and grasslands and riverine woodlands. Rural livelihood sources across the MIDA landscape are diverse. These include farming, fishing, tourism, arts, and crafts. The Okavango sub-district in north-western part of Botswana is a malaria and schistosomiasis endemic area. Anthropogenic pressures may lead to increased transmission, vector borne diseases episodes, persistent use of and resistance to pharmaceutical drugs and pesticides.

Data collection methods

Data were derived from a participatory rural appraisal workshop consisting of 50 intergeneration community members comprising of youth [10], men [15] and women [25], and non-obtrusive field observation in Shakawe, the study site.

During the workshop, participants were asked to free list emerging they consider to pose an environmental threat to the environmental integrity of the Okavango Delta. The brainstorming exercise was followed by and environmental issue prioritization through improvised “Likert scale bean allocation” system.

Emerging themes

Emerging themes were the destruction of the environment by elephants, desiccation of the river, forest fires, recurrent droughts, poor waste management, environmental degradation, and human wildlife conflict. They pointed the urgent need to address poorly managed Shakawe waste disposal site which poses a threat to people’s sources of livelihoods such livestock farming and a convenient resting place for malaria vector mosquitoes. Closeness of homesteads to breeding sites expose fisher and flood recession farmers to mosquito bites. Regarding the latter, Shakawe has a health facility which provide drug treatment for a range of health conditions including malaria. Residents often go to the clinic for treatment but also tend to consult traditional health practitioners. Consequently, some quantities of drugs obtained from the clinic may be used whereas other drugs may be disposed unused. This potential pharmaceutical waste henceforth become an integral part of household solid waste that ultimately find its way to the unmanaged dump site.

Concluding note

Systematic community, household surveys and/or case studies are needed to follow up on issues specifically related to disposal of pharmaceutical waste from health facilities and households in the Okavango region including potential impacts on the environment.

8 Medicine Regulation and Regulatory Harmonization

8.1 *African Medicine Regulatory Harmonization: Experience from Tanzania*

Adam Fimbo

DG Tanzania Medicines and Medical Devices Authority (TMDA), Dar Es Salaam, Tanzania, e-mail: adamfimbo@gmail.com

The African Medicines Harmonization Programme (AMRH) is the programme of African Union implemented as part of the Pharmaceutical Manufacturing Plan for Africa (PMPA) initiative. The programme was introduced in 2009 and covers all Regional Economic Communities (RECs) in Africa. Within East African Community, all National medicine regulatory authorities (NMRAs) are part of the programme.

The overall East Africa Community Medicines Regulatory Harmonization (EAC MRH) programme goals are to harmonize regulatory requirements in the region. To date all relevant technical guidelines and requirements have been harmonized and NMRAs are working jointly in dossier assessment and good manufacturing practice (GMP) inspection activities.

A number of products have so far been registered and many factories jointly inspected for compliance to GMP requirements.

Accrued benefits of the programme todate embraces:

1. Streamlined regulatory approach
2. Lead time reduction
3. Reduced duplication of efforts
4. High level of staff competence
5. Products approved for common market
6. Quality, safety and efficacy of products assured

Together with the human medicines' harmonization initiative and in tandem with the same spirit, the programme for harmonizing requirements for regulation of veterinary medicines is likewise underway. The mutual recognition procedure has been endorsed by all NMRAs in EAC.

Within the Southern African Development Community (SADC) region the same has been achieved.

9 Case studies on screening methods for medicine quality analysis

Julia Gabel[1], Gesa Gnegel[1], Patric Proches Kimario[2], Lutz Heide[1]

[1] Pharmaceutical Institute, University of Tübingen, Germany, e-mail: heide@uni-tuebingen.de

[2]Tanzania Medicines & Medical Devices Authority, Arusha, Tanzania,
e-mail: proches.kimario@tmda.go.tz

In the fight against the proliferation of substandard and falsified medicines, simple low-cost screening devices can substantially contribute to an early detection of poor-quality products and thereby to a prevention of harmful effects on the patients. In Part I of the exercises/case studies, J. Gabel invited the participants to test a smartphone app recently developed under her participation and named “TLCyzer” [1]. The app is intended to allow a more accurate quantitative evaluation of the results of thin-layer chromatographic (TLC) analyses of medicines, e.g. using the GPHF Minilab. For the application of this method, a locally producible wooden box has been designed which ensures TLC photography under standardized conditions and shielding from ambient light. Photography and quantitative image analysis are then carried out with Android-based smartphones. The app is available free of charge as General Public License (GPL) open-source software, and interested individuals or organizations are welcome to use and/or to further improve this software.

In Part II of the exercises/case studies, G. Gnegel invited the participants to use a low-cost hand-held near-infrared spectrometer (NIR-S-G1; InnoSpectra, Taiwan [2]) in combination with the manufacturers’ free “ISC NIRScan” app to quickly record spectra of some unlabeled white tablets, and to determine whether they contained co-trimoxazole, penicillin V or ciprofloxacin, or none of these agents. She also gave a brief introduction into the basic principles of NIR spectroscopy and of multivariate data analysis of the resulting spectra using principal component analysis (PCA), which is part of her current PhD research project.

Finally, in Part III of the exercises/case studies, P. Kimario explained the risk-based post-marketing surveillance approach used by the Tanzania Medicines & Medical Devices Authority (TMDA) for quality testing in a resource-limited setting. He subsequently invited the participants to visit the TMDA Arusha office of which he is head. There, he and his colleagues demonstrated the use of the Minilab of the Global Pharma Health Fund [3] in the post-marketing surveillance of medicine quality, a procedure routinely employed by TMDA since 20 years [4].

Figure 5: Demonstration of the GPHF Minilab to the workshop participants in the Arusha TMDA office (© TMDA)

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Helmholtz Centre for
Environmental Research – UFZ
Permoserstraße 15
04318 Leipzig I Germany
www.ufz.de

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