Novel approaches to the detection of substandard medicines

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Dekan

“Do not go where the path may lead,

***go instead where there is no path and leave a trail**.”*

Ralph Waldo Emerson

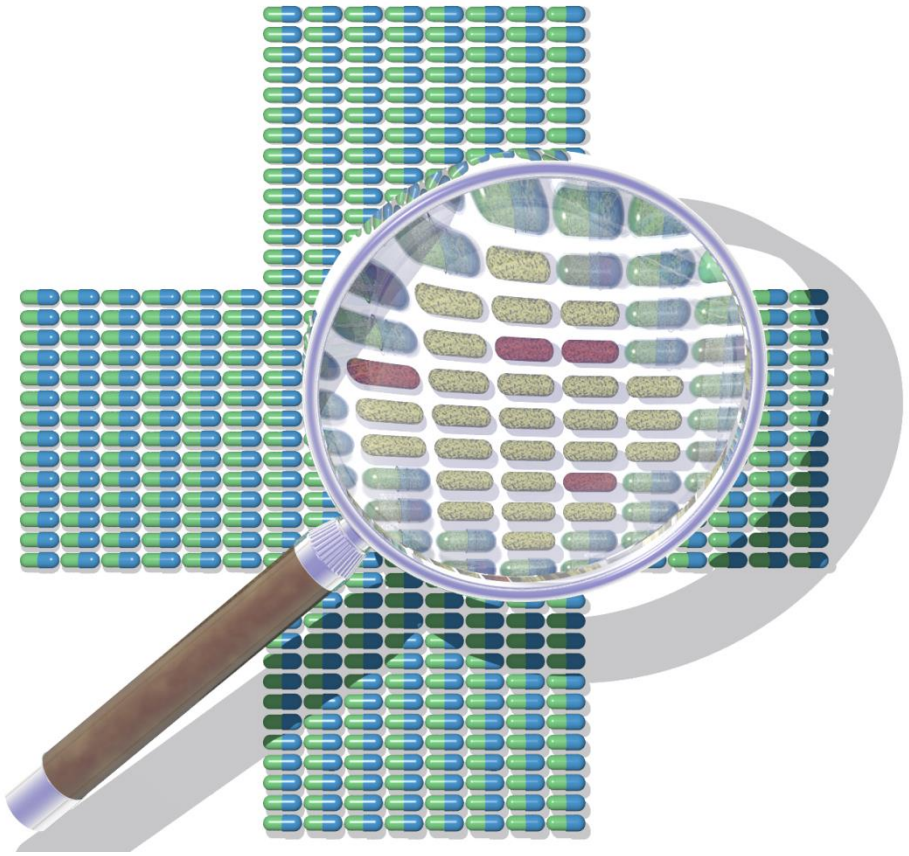
“Things take longer to happen than you think they will,

and then they happen faster than you thought they could.”

Ruedi Dornbusch

The research presented in this thesis

is dedicated to my dearest grandmother



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„**Leider läßt sich eine wahrhafte Dankbarkeit mit Worten nicht ausdrücken**."

Johann Wolfgang von Goethe

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Abbreviations

ACRONYM	DESCRIPTION
ACT	Artemisinin Combination Therapies
CE	Common Era
AE	Adverse event
AiBST	African Institute of Biomedical Science & Technology
AIDS	Acquired immune deficiency syndrome
API	Active pharmaceutical ingredient
APQR	Aggregate Product Quality Review
BCE	Before Common Era
BMI	Body mass index
BPh	British Pharmacopoeia
BU	Boston University
CCD	Charge coupled device
CD3	Counterfeit detection device number 3
CE	Capillary electrophoresis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CODFIN	Counterfeit Drug Forensic Investigation Network

CWGH	Community Working Group on Health
DART	Direct analysis in real time
DEC	Drug-Event Combination
DESI	Desorption electrospray ionization
DHA	Dihydroartemisinin
DHIS2	Zimbabwe District Health Information System 2
DANN	Deoxyribose nucleic acid
DOJ	Department of Justice
DR	Dissolution rate
DSUR	Development Safety Update Reports
EB05	Lower confidence limits for the Empirical Bayes Geometric Mean
EBGM	Empirical Bayes geometric mean
EMA	European Medicines Agency
EMP	Essential Medicines and Health Products
FID	Flame Ionization Detector
FDA	Food and Drug Administration
GC	Gas chromatography
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GPvP	Good Pharmacovigilance Practice

GSK	Glaxo Smith-Kline
GxP	General abbreviation for good practice quality guidelines and regulations
HAI	Health Action International
HCP	Health care professional
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonization
ICSR	Individual case safety report
ID	Identity
IRMS	Isotope ratio mass spectrometry
JP	Japanese Pharmacopoeia
LC	Liquid chromatography
LLT	Lowest level term
LMIC	Low and middle income country
LoE	Lack of efficacy
MAH	Market authorization holder
MCAZ	Medicines Control Authority of Zimbabwe
MedDRA	Medical dictionary for regulatory activities
MEDQUARG	Medicine Quality Assessment Reporting Guidelines
MGPS	Multi-item gamma poisson shrinker
MHRA	Medicines and Healthcare products Regulatory Agency

MOH	Ministry of Health
MQDB	Medicines quality database
MS	Mass spectrometry
MSSO	Maintenance and Support Services Organization
NECC	New England Compounding Center
NGO	Non-governmental organizations
NHS	National Health Service
NIR	Near-infrared
NMR	Nuclear magnetic resonance spectroscopy
NOS	Not otherwise specified
NMRA	National Medicines Regulatory Authority
NRRA	National or Regional Regulatory Authority
ODR	Observation of disproportional reporting
PIM	Pharmacist initiated medicines
PP	Prescription preparation
QD	Quality defects
PSUR	Periodic Safety Update Reports
PT	Preferred term
PV	Pharmacovigilance
RDT	Rapid diagnostic test
RMP	Risk management plan

RP-LC	Reverse-phase liquid chromatography
SAE	Serious adverse event
SAS	Statistical analysis software
SAV	Safety and vigilance
SD	Standard deviation
SMQ	Standardized MedDRA® Query
SOC	System organ class
SSFFC	Substandard/spurious/falsely-labelled/falsified/counterfeit
SSM	Substandard medicines
TLC	Thin layer chromatography
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UN	United Nations
UNICEF	United Nations Children's Fund
UPLC	Ultra-performance liquid chromatography
US	United States
$US	United States Dollar
USP	United States Pharmacopoeia
UV spectrometry	Ultraviolet spectrometry
WHO	World Health Organization
XFR	X-Ray fluorescence

XRD	X-Ray diffraction
FTIR	Fourier-transform infrared spectroscopy

I Summary

The research projects described in this thesis were conducted in a joint industry-university cooperation between the Patient Safety department of Novartis Pharma AG and the division of Clinical Pharmacy and Epidemiology at the University of Basel. This dissertation covers the topic of substandard medicines (SSMs), a global health issue (1) that is underestimated and inadequately understood due to its complexity (2). Substandard medicines are licensed medicines (3), either innovator or generic (4) that most commonly contain either too little or too much active pharmaceutical ingredient (API) (4). SSMs may be the result of negligence, error and/or low standard of quality control (QC) of the manufacturing process (non-good manufacturing accredited status) or distribution process (degradation of medicinal products through bad storage) (5).

The use of SSMs may result in severe adverse events (AEs) and even death (6) and may promote antimicrobial resistance (4). The presence of SSMs is not unique to developing countries (6) as there are examples of SSMs in Iceland (7), Portugal (8) Canada (9) among others. This issue afflicts vulnerable patient populations worldwide (1).

However, the true extent of this hazard is unknown as systematic and comprehensive prevalence studies are lacking to date (10). There is a shortage of robust evidence of SSMs (11) as reports on SSMs are often found in "grey literature" and newspapers (12). Estimates are primarily available for antimicrobial medicines (13,14). The existence of SSMs may be a result of weak regulatory systems and limited access to medicines in many countries (12). Due to their similarities SSMs and falsified medicines are usually seen as one and the same problem, however in many aspects they are independent problems that require different solutions (15). While falsified medicines are illegal, unlicensed and are manufactured deliberately to deceive as to source and content (i.e. they often contain minimal or no active pharmaceutical ingredient), SSMs result from manufacturer`s "negligent breach of regulator's legal requirements" (16) such as error in manufacture or distribution (17).

Globalization and parallel imports in Europe have substantially contributed to the existence of an increasingly (18) complex pharmaceutical supply chain (19). "Medicines constantly change hands between production and dispensing to the patient" (20) (through

manufacturers, importers, wholesalers) and the multiple transactions facilitate falsified and substandard medicines to penetrate the global legitimate medicine supply chain (21,22). Regular QC and post-marketing surveillance of pharmaceuticals have been a critical challenge for countries of the developing world ever since (23) and the detection of SSMs (24) is difficult as they do not usually differ in appearance but are characterized mainly by altered chemical content and reduced bioavailability of the active pharmaceutical ingredient (14).

My thesis addresses the serious implications of SSMs to public health care and describes attempts to bridge the apparent gap of detecting SSMs (25) by exploring new detection approaches in pharmacovigilance and in analytical technologies as well as validating these methods in field studies.

Currently SSMs are only identified by analytical devices (26). Because of their high costs and portability issues (26) most of the analytical technologies cannot be used in resource-limited countries. Evidence of high increases of SSMs, predominantly in developing countries, reveals that there is a need for easy, rapid and affordable detection tools (27). Currently, there is no portable screening device in the market that can accurately measure the content of active pharmaceutical ingredients (API) of medicinal samples (28). The only available device is PharmaChk, an innovative analytical instrument in development that is able to quantify the amount of a number of APIs (e.g. artemisinin, tetracycline) and evaluate their dissolution profile (29). In collaboration with the Biomechanical Department of Boston University, we conducted further research on this device and the assay for essential antimalarial drug Coartem® (artemether and lumefantrine) (30) was developed and used for a field study in Zimbabwe.

In addition to analytical detection, pharmacovigilance signal detection techniques have been shown to be effective in detecting SSMs. Preliminary research conducted by the WHO Uppsala Monitoring Centre (UMC) exists on using data mining algorithms on the WHO Vigibase® data set of global individual case safety reports (ICSRs) to identify SSMs (31).
In my thesis this preliminary research was validated and further extended by using the empirical Bayes multi-item gamma poisson shrinker (MGPS) disproportionality algorithm.

We conducted three different stratification analyses using 24 preferred terms (PTs) indicative of defective medicines. A cut-off of EB05 [lower confidence limits for the Empirical Bayes Geometric Mean (EBGM)] (32) greater than two was used to identify clusters of SSMs. We were able to not only confirm clusters of ethinylestradiol and salbutamol identified by the UMC in 2014 (33), but we also found evidence of a substandard rivastigmine patch which resulted in advisory letters to health care professionals from an independent organisation of pharmacists working in support of the Competent Authority in the Netherlands.

After validation of this pharmacovigilance screening tool and the assay of Coartem® on the PharmaChk device and in order to assess the efficiency of these two detection approaches of SSMs in real world practice, we initiated a field study on Coartem® and its generic versions in Zimbabwe. Malaria is a major health burden in Zimbabwe with 8,000,000 people at risk (50% of the population) (34). Previous studies have shown that Zimbabweans are at high risk from substandard and falsified medicines, resulting in increased mortality, morbidity, financial strain and long-term antimicrobial resistance (35–37). We collected samples from sites of the private health sector that were randomly selected as well as from sites that were conveniently accessible. The purchase of samples where sellers were blinded to the intent of our research was performed in 18 cities in areas with high risk for malaria in Zimbabwe.

The quality of purchased samples was tested through qualitative and quantitative measurements using different screening field devices including Raman, Near-Infrared (NIR) spectrometry and X-Ray Fluorescence (XFR) as well as spectrophotometer and high performance liquid chromatography (HPLC) analysis for confirmatory analysis in analytical laboratories in Zimbabwe, Switzerland and the United States (US). Data mining for the antimalarial drug Coartem® identified no excess reporting of AEs related to Coartem® in Zimbabwe. No data on the registered generic versions of Coartem® in the Vigibase® database (38) was available for Zimbabwe.

Analyses of all screening and confirmatory analytical technologies revealed a good quality of all collected samples. The PharmaChk device demonstrated comparable results of the

collected samples to the gold standard method, which is HPLC. The analytical screening tool PharmaChk was able to determine that there was no unexpected risk with essential medicine artemether/lumefantrine in Zimbabwe. This pilot study highlighted the potential of these two detection methods. However, further research on a larger scale of samples and other therapeutic areas is required to validate these findings. Moreover, the proposed flowchart (Figure 23) includes both detection methods to triage suspected medicinal samples for further confirmatory testing which may result in reduction of resources, analysis time and money. Both tools can be applied by multiple and diverse stakeholders. The pharmacovigilance detection tool can be targeted by regulators, NGOs and manufacturers whereas the PharmaChk device can be used by healthcare professionals (HCPs) in hospitals, pharmacists, manufacturers and customs officers.

This thesis highlights the need and importance of collaborations in identifying SSMs. Without the partnership between academia, industry and private laboratory institutions this research may have not been possible. The complex issue of SSMs requires this kind of engagement to enhance safe and effective medical treatment by decreasing the number of circulating SSMs worldwide.

II Introduction

A high quality of medicines is a characteristic that is often taken for granted (39). Over time, drug development has led to an increasing importance of quality as demonstrated by the implementation of universally accepted laws in healthcare systems worldwide. One of the UN targets the year 2030 is to "achieve access to safe, effective, quality and affordable essential medicines and vaccines for all" (35,40).

Medicines are used to treat, cure, or prevent diseases. According to the WHO "all medicines must meet three criteria: be of good quality, safe and effective" (41). All authorized (licenced) medicines must meet a documented quality specification, and there should be a positive benefit to risk assessment, such that the benefits outweigh the potential harms (42). The distribution of medicines with low quality and/or safety has become a global threat and the use of low quality medicines may have severe impact on public health (43). Patients may suffer from serious adverse events (SAEs), treatment failures due to drug resistances, and in the worst case scenario, death (44). Moreover SSMs ("refer to medicinal products that do not meet the quality specifications given in the accepted pharmacopoeia" (45) [Chapter 2] may lead to the loss of patient's confidence in medicines and in the healthcare system (46). The consequences do not only affect the end users (patients) but all stakeholders involved in the medicines supply chain. Use of drugs with poor quality may result in a financial loss for patients and their families, the healthcare system and the pharmaceutical manufacturers. In addition it may involve increased burden for HCPs, regulatory authorities, and customs officers (47).

Literature search on "counterfeit" medicines reveals that there are "guidelines for development of measures to combat counterfeit drugs" (48) as well as the "EU Falsified Medicines Directive"(49) and significantly more research articles on falsified medicines than there are on SSMs (50).

The prevalence of poor quality medicines worldwide is not known, but the increase in the number of quality defect reports on SSMs is alarming (51). According to Nayyar et al. (52), the testing results of 16,800 samples of antimalarial drugs, anti-tuberculosis medicines,

antibiotic and anti-leishmaniasis drugs in seven studies showed that 9-41% failed to meet quality standards. Cases are not only reported from emerging market countries (Sub-Saharan African countries as well as Asian and Latin American regions) (53) (54). A retrospective review of drug alerts and drug recalls issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (2001-2011) [UK] performed by Alumzaini et al. (55) revealed that there were 280 SSMs of which 222 were recalled mainly due to contamination of parenteral formulations (74 incidents) and issues relating to packaging (98 incidents). The number of SSMs in UK increased 10 fold from 5 incidents in 2001 to 50 incidents in 2011 (55).

The supply chain for medicines worldwide delivers high quality medicines to patients but also an increasing amount of SSMs that is dispensed by unlicensed pharmacies, hospitals, illicit medicines outlets or can be purchased through unregulated websites. SSMs are difficult to detect as usually they cannot be detected by appearance, "however they often fail to properly treat the disease or condition they were intended" (44). Currently defective medicines can only be properly identified using analytical methods (56). In general many detection instruments verify the presence of the main API and therefore mainly focus on "counterfeit" medication. In order to identify SSMs, devices able to perform quantitative analysis for determination of impurities and amount of main ingredients are required (57).

Aims and Scope

The primary focus of my research described in this thesis are SSMs. However in literature, SSMs are often conflated with falsified medicines which makes it crucial to differentiate between SSMs and falsified medicines (14). While falsified medication results from a "deliberate or intentional act to mislead any person concerning a medical product", substandard medications may also emerge from unintentional errors in the manufacturing process by licensed producers or degradation that occurs within in the supply chain (58).

The aim is to investigate innovative statistical and analytical detection methods for identifying SSMs in developed, as well as in low-income countries (Sub-Saharan African countries as well as Asian and Latin American regions), as well as contribute to efforts of the

scientific community undertaken globally to ensure access to medicines of good quality and with a favourable benefit-risk assessment for patients worldwide.

The application of the presented statistical and analytical detection methods will allow health authorities, pharmaceutical companies and pharmacies both in developed as well as resource-limited countries to identify SSMs even before they would be dispensed to patients.

This thesis is divided into the following parts: After the background section on SSMs (Chapter 1-6) which gives an overview on SSMs, including the epidemiology, the delimitation to falsified medicines and the worldwide impact on public health,

Part 1 (Chapters 7-8) illustrates a statistical approach using pharmacovigilance tools to detect SSMs. A non-analytical detection tool was introduced by Uppsala Monitoring Centre (UMC) in 2011 in the Monitoring Medicines project (59). Preliminary research exists on using data mining algorithms on spontaneous reports to identify poor quality medicines (60). In this thesis this preliminary research was validated and further extended by using a different statistical methodology.

Part 2 (Chapter 9) refers to the analytical screening tool PharmaChk to identify poorly manufactured medicines especially in emerging countries. Most of the commonly used analytical devices to identify SSMs cannot be used in resource limited countries. The main reasons are bulkiness of the instruments, the high price and the lack of trained personnel (61). To address the need of detecting SSMs in low-income countries, we assessed the efficiency of the PharmaChk device in Zimbabwe by comparing it to the gold standard method HPLC.

Part 3 (Chapters 10-12) describes an ongoing pilot field study performed in Zimbabwe to identify potential substandard and falsified antimalarial medicine samples of fixed-dose combination drug of artemether and lumefantrine (coartemether) sourced from the private sector. This study used the pharmacovigilance tool outlined in Part 1 and the quantitative screening device PharmaChk described in Part 2.

Chapters 13-15 present the final discussion, future outlook and overall conclusion of this research project.

For the purpose of this thesis, the term “falsified medicines” will be used instead of “counterfeit medicines” as these are associated with intellectual property legislation and trademark protection. In addition the terms drug, medicine and pharmaceutical products are used interchangeably to refer to medicinal products intended for prophylactic, diagnostic or therapeutic use as well as poor quality medicines and defective medicines (62).

III Background

1 History of SSMs

The concern about the quality of medicines is an ancient problem. There have been writings from the fourth century before Christ (BCE) on the dangers of adulterated drugs and in the first century Common Era (CE) the Greek physician Dioscorides described detection methods of these products in his Materia Medica (63,64). Despite all the advances in regulations for medicines quality over a millenium, history reveals tragic consequences of SSMs (65).

In 1901, the standard treatment for children with diphtheria was an antitoxin derived from the blood serum of horses. The serum of a horse who contracted tetanus was accidentally bottled and used to treat diphtheria patients, causing the death of 13 children. The serum had been manufactured in local establishments with no uniform quality controls in place to ensure potency and purity. In addition no analysis of the final antitoxin was performed. At the same time a similar tragedy occurred in Camden, New Jersey, where nine children died from tetanus after receiving contaminated smallpox vaccine. These two tragedies led to the adoption of Biologics Control Act (first "Virus-Toxin Law") in 1902 (66).

Another example of fatal consequences of SSMs dispensed to patients occurred 35 years later. In 1937 more than 100 patients, most of them children, died in 15 US-States because of being exposed to a poisoned by elixir of sulfanilamide, a new formulation which had not been analyzed for toxicity, as this at the time was not legally required. It contained 10% solution of sulfanilamide to treat streptococcal infections and 72% diethylene glycol used as solvent which turned out to be the lethal ingredient (67). All patients exhibited kidney failure symptoms and intense pain. The manufacturer was unaware of the toxicity of diethylene glycol (68). This incident led to the enactment of the Federal Food, Drug, and Cosmetic Act on 25th June 1938 which obliged manufacturers to assure the safety of a drug before it could be marketed by Food and Drug Administration (FDA) (69,70).

The course of history reveals that "many human lives have been sacrificed by failure to meet the standards" (71) of good quality medicines. The aforementioned tragedies should serve as a warning. It was 1985 at the conference on the rational use of drugs in Nairobi when the problem of poor quality medicines was brought to the attention of international regulatory community (63,72).

Unless adequate medicine quality standards are not put into effect, several more lives or injuries among public are exposed to risk every day. "Any essential compromise with these requirements will inevitably exact a toll of deaths or injuries among the public. The life and safety of the individual should not be subordinated to the competitive system of drug exploitation" (71).

2 Definition debate of substandard and falsified (SF) medicinal products

The controversial topic of terminology of what is SSM, falsified or counterfeit medicines has created lots of confusion (73) among the world scientific community as to date there are no universally agreed legal definitions available (74). A variety of definitions exist in many countries due to the "influence of the native languages as well as the preexisting local legal terminology" (75). Although the burden of SSMs on public health has been present and known for many centuries, the first definition of SSMs was introduced by the WHO as recently as 2011, whereas counterfeit medicines were first defined in 1992 (76).

In 2010 the WHO introduced the wording SSFFC (substandard, spurious, falsely labelled, falsified and counterfeit) medicinal products which combined SSMs and falsified medicines into one category (77,78). Since 29th May 2017 the definitions for "Substandard and Falsified medical products" were revised at the Seventieth World Health Assembly. The term "SSFFC" has been replaced by "Substandard and Falsified medical products"(79). Moreover in all future documentation the terminology "falsified" will be used instead of "counterfeit" in order to prevent trademark infringement (73). According to Michael Deats, Group Lead of the Safety and Vigilance (SAV) team at the WHO (80), all member states have approved the revised definitions (81).

The definitions of poor quality medicines introduced by WHO have been grouped into three categories (82):

Substandard: Also called "out of specification", are authorized medical products that fail to meet either their quality standards or specifications, or both." According to Michael Deats (80,81) degraded medicines also fall into the category of SSMs (81). Moreover the deliberate production of SSMs by authorized manufacturers should be considered "falsified" (82).

Unregistered/unlicensed: Medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority (NRRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Falsified: Medical products that deliberately/fraudulently misrepresent their identity, composition or source. When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition, or source, then the medical product should be considered "falsified".

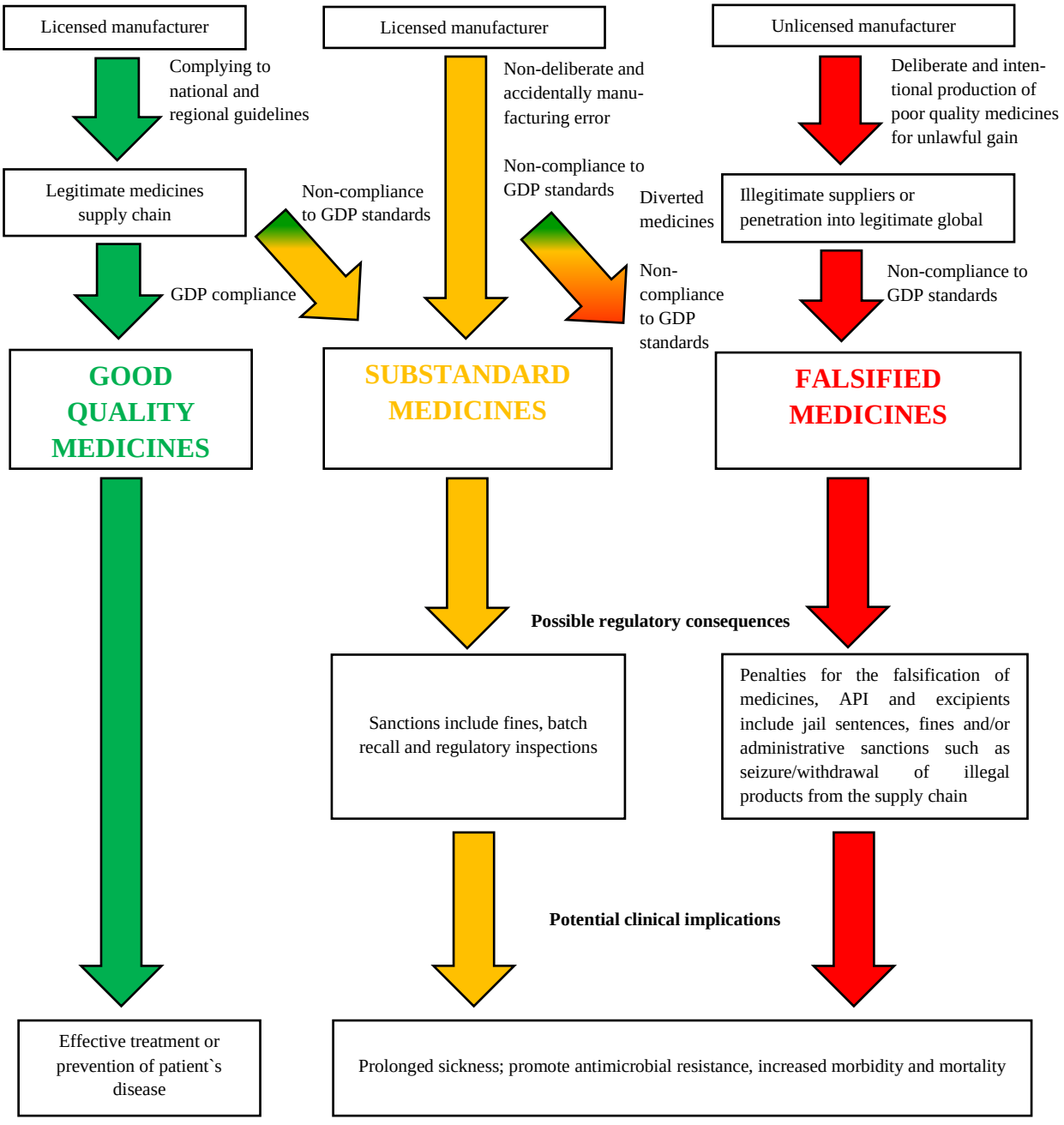
The WHO anticipates that all stakeholders will adopt these new definitions to allow accurate analysis of data and combat more effectively against substandard and falsified medical products (79). Ongoing definition debates from 1992 until present on "counterfeit" drugs reflects the concerted effort of WHO in developing and coordinating various resolutions, sophisticated initiatives and international cooperation to tackle medicine counterfeiting (83) whereas there have been only limited endeavors on the field of SSMs (84). Universally agreed definitions are crucial to understand the magnitude of this global issue (85). The absence of commonly agreed definitions impedes the development of solutions to fight against this major challenge of falsified and SSMs.

3 Differences between substandard and falsified medicines

Good quality medicines comply with good manufacturing (GMP) and good distribution practice requirements (GDP) and lead to effective treatment and prevention of diseases. As mentioned in the chapter above the terms "substandard medicines and falsified medicines" have often been

conflated and in most scientific articles have been used interchangeably (14,78,86). Although there are many similarities between the two categories, they “have different origins and different solutions” (87). SSMs represent a worldwide health impediment in developed and developing countries for both branded and generic medicines, however the precise extent of the hazard is still unknown (78) [Chapter 4].

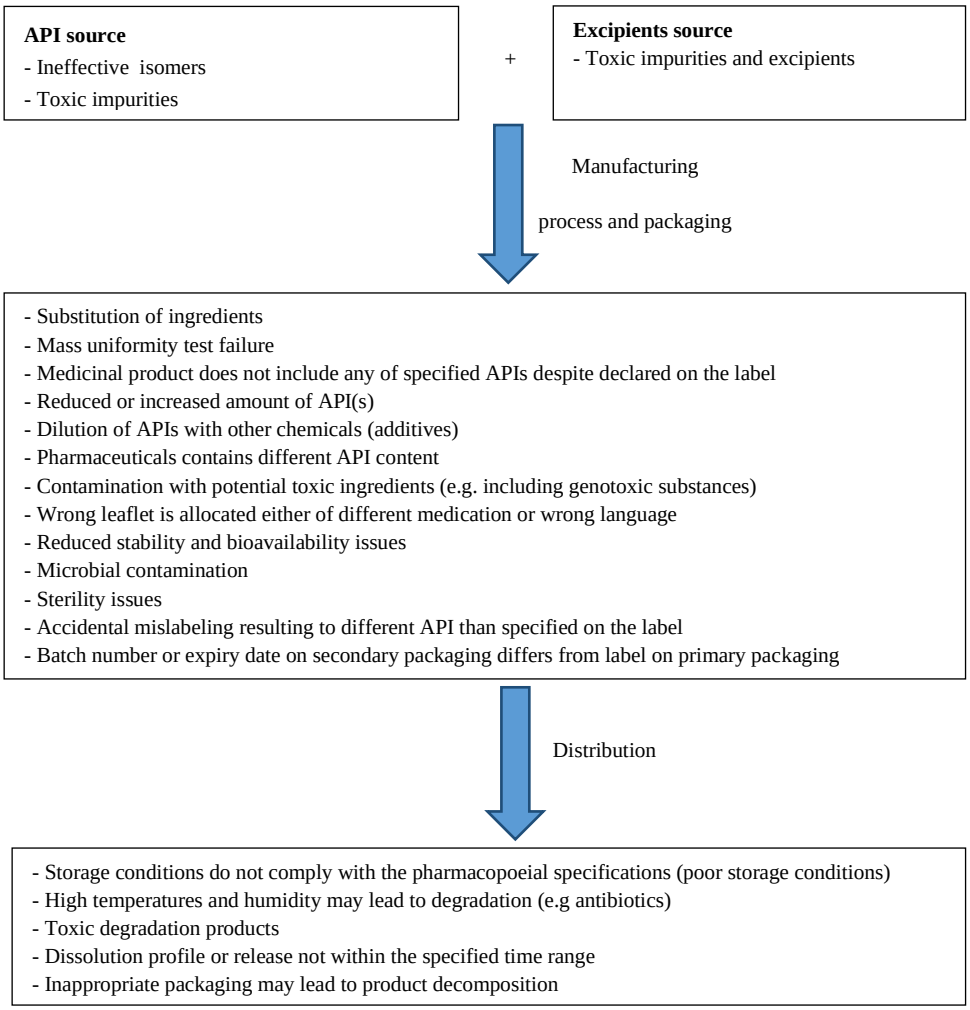
Figure 1 Differences between good quality, substandard and falsified medicines (4,88,89,90)



For the clear distinction of the two terms it is crucial to distinguish between deliberate and intentional production of falsified medicines versus non-deliberate and accidental manufacturing error of SSMs [Figure 1] (91). While “falsified medicines can be considered as being substandard” (82,92), not necessarily all SSMs can be denoted as falsified (93). The accidental manufacturing of SSMs or degradation of medicinal products due to exposure to heat for example are errors or

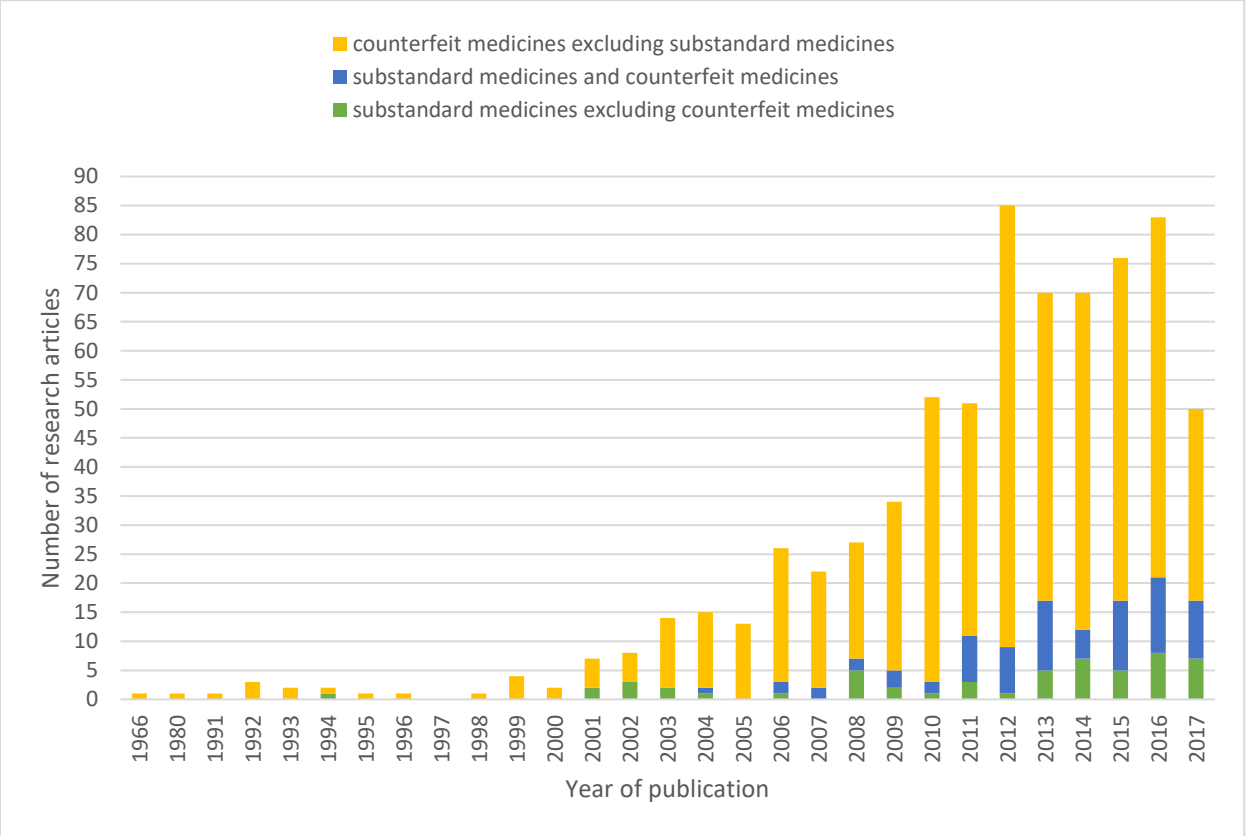
accidents which are surely negligent but do not represent a serious crime (93). A regulatory inspection as a response could be an appropriate measure to enable the manufacturer to comply with good GxP practices in the future. In contrast, the intentional production of unregistered medicines and SSMs, leading to the release of falsified medicines, is a serious public health crime and requires criminal sanctions (16). As SSMs may result from accidental non-compliance with GMP and GDP practices there is a broad variety of deficiencies in manufacturing and distribution processes (4) (Figure 2 below). Medicinal products "that were originally of good quality may degrade and become substandard during routine transport and storage, especially if stored beyond their expiry date and if exposed to extremes of humidity and temperature" (6). The retrospective analysis of 128 quality defects (including reports on falsified medicinal products, rapid alerts, reports of products with statements of non-compliance with GMP, reports of withdrawal of certification of suitability and warning letters) received by European Medicines Agency (EMA) in 2016 revealed that the most reported causes for SSMs were manufacturing laboratory controls issues (out of specification test results) (53%) and product label issues (47%) (94).

Figure 2 Quality defects resulting in SSMs (4,95) (16)



There is much more attention and awareness on falsified medicines than on SSMs (6). This can be seen by the existence of various global initiatives concerning falsified medicines since 1992 (76), funded by health authorities and the pharmaceutical industry (96) as well as by the number of published scientific articles (50). The analysis of the literature portal PubMed (97) in August 2017 showed the presence of 588 research articles on the topic of "counterfeit medicines" since 1966 whereas only 54 research articles on SSMs were published from September 1994 - September 2017 (Figure 3). The graph (Figure 3) below also demonstrates that most of the scientific research was conducted after year 2000 for both falsified medicines and SSMs.

Figure 3 Research articles on substandard and "counterfeit medicines" until September 2017



4 Widely unknown estimate of epidemiology of SSMs

There is insufficient data in the scientific literature to determine the precise estimate of prevalence of SSMs distributed worldwide (10,98,99,100). It has been suggested in the literature that the majority of reported SSFFC medicines were substandard, failing API content and dissolution/disintegration tests, rather than counterfeit (101). To accurately determine the prevalence of SSMs, there have been limited number of studies using random sampling techniques and covert approach (14,99). Data exist on only few pharmaceutical classes including antimalarials, antibiotics and antiretrovirals (14). No prevalence study has been performed in developed countries although number of medicinal recalls have risen dramatically in the last decade (9,55). The following three review articles provide a comprehensive overview on existing prevalence studies on SSMs and their results.

Considering the timeframe 1948-2013, Almuzaini et al. (13) identified 44 studies predominantly on antimicrobial medicines in 25 different lower middle-income countries. Only 15 of these studies

met the quality assessment criteria from the medicine quality assessment reporting guidelines (MEDQUARG) checklist (11). Most of the studies did not distinguish between substandard and falsified medicines. The median prevalence of falsified or SSMs was about 28.5% with a large range between 11-48%. They concluded that the prevalence of poor quality samples sourced from unlicensed outlets was significantly higher than those procured from licensed outlets from the public and private health sector. Moreover most of the SF samples contained inadequate amounts of APIs. No prevalence data was found in high-income countries (13).

Similar findings were shown in a meta-analysis conducted by the U.S. Pharmacopoeial Convention on the publicly available medicines quality database (MQDB) for the period of 2003-2013 in 17 countries of Africa, Asia, and South America. Out of 15'063 collected medicine samples, 767 samples were of substandard quality (90.4%). Overall, a failure rate of 11.5% was observed in South America, 10.7% in Africa and 3.5% in Asia. Antimalarial, antibiotic and antituberculous medicinal products revealed the highest distribution of SSMs by therapeutic indication (102).

Torloni et al. reviewed the quality of oxytocin and determined that the median prevalence of samples that failed the quality analysis was 45.6% in a range of 0-80%. They found that more than one third of the acquired samples from 15 countries of Asia, Africa and Latin America were substandard due to insufficient API content (<90%) (103).

The reviews reveal that due to the paucity of data it is very difficult to determine the accurate prevalence of SSMs (104). The prevalent data is biased towards antimicrobials particularly antimalarials (104). Moreover the prevalence results need to be interpreted with caution as many of the studies were conducted with inadequate sampling designs such as convenience-based sampling, insufficient sample sized and standardized chemical analysis techniques and instruments (104,105). In addition these estimates vary by time and place (106). Surveys with strong methodology are conducted in various therapeutic indications including non-communicable chronic diseases and specific countries (107) are required to better understand the scale/magnitude of the problem (13,99,104).

5 Adverse health outcomes and societal effects of SSMs: Quality of medicines matters (4,108-109)

Since SSMs have a multifaceted origin, these may lead to various adverse health outcomes including treatment failures (due to lack of efficacy), increased mortality (for the same reason) and support of promulgation of resistances (4,110-111).

The serious illness burden generated by these medicines is insufficiently quantified. Fernandes et al. indicated that SSMs contribute to over 100,000 preventable deaths annually (111). The first evidence-based estimate (106) was provided by Renschler et al in 2009. They estimated that the deaths of 122,350 children under-five suffering from malaria were associated with consumption of poor-quality antimalarials, representing 3.75% of all deaths in children under five years of age in their sample of 39 countries in Sub-Saharan Africa (105). Most of the deaths caused by SSMs involved the contamination with diethylene glycol (67–71).

The analysis of scientific literature in addition to the 27 WHO medical product alerts on defective medicines from 1989 until now reveals that there have been many reports of serious clinical AEs and fatalities. Principally, the causes can be categorized into seven groups. In the following Table 1these are described with illustrative examples highlighted (4,95).

Table 1 Causes and outcomes of SSMs based on examples

Clinical outcomes of SSMs	Incidence example
Intoxication through contamination of the active pharmaceutical ingredient (API)	In January 2013 two types of locally produced cough syrups led to 50 deaths in Pakistan due to contaminated API dextromethorphan with varying levels of levomethorphan which is an opioid analgesic. Eight months later, reports of suspected dextromethorphan intoxication appeared from 44 patients in Paraguay who had developed serious adverse reactions including seizures and respiratory distress and one death. The Paraguayan authority revealed that the API dextromethorphan was procured in the same laboratory in India that was used by the cough syrup manufacturer in Pakistan and the batch number resembled. Samples of both incidents did not fulfill the specific optical rotation requirement of the International Pharmacopoeia (112).
Contamination with impurities and additives not declared on the label	In January 2012, there was a serious incident with 125 deaths and more than 450 cardiac patients with fatal AEs in Pakistan as a result of fatal bone-marrow suppression after taking the inadvertent tainted isosorbide 5 mononitrate contaminated with an excessive dose of pyrimethamine (113–115).
Sterility issues through microbial contamination	In September 2012, there was the largest outbreak of fungal meningitis in several states in US due to bacterial and / or fungal contaminated steroid injection prepared by New England Compounding Center (NECC) in Massachusetts. This incidence lead to 751 cases of fungal meningitis, stroke, spinal or paraspinal infection and 64 deaths (116,117). In the case of fungal meningitis as described above, therapy had to be continued for at least 6 months and few patients had to remain on long-term therapy.

Mislabeling	In 2001 there were reports of deaths of two premature infants after receiving injections of potassium chloride instead of glucose 5% / 10ml sterile solution due to mislabeling of the medicinal product (118).
Insufficient or excess amount of correct API than stated on the label	After the administration of substandard propofol in Zambia in 2015, patients experienced various AEs including urticaria, bronchospasm and inadequate depth of anesthesia. The laboratory analysis concluded that none of the analyzed vials contained the declared amount of propofol (119).
Non-compliance with dissolution tolerance limits (bioavailability) (14)	According to Leslie et al. 2009 the locally manufactured generic sulfadoxine/pyrimethamine tablets, sourced due to shortages of Fansidar, contributed to malaria epidemic in a refugee camp in Pakistan. The dissolution profile (120) of the generic tablets did not comply with the stated tolerance limits, therefore the tablets were not released at the required dose (121).
Unstable formulation	The study of Mastoraki et al. showed a higher incidence of post-operative infections in adult patients undergoing coronary artery bypass grafting surgery after receiving generic version of cefuroxime. The reason for this clinical implication was the use of substandard generic antimicrobial prophylaxis resulting from the degradation of the generic formulation into two ineffective parts (120).

In addition to the clinical implications the unintentional use of SSMs will presumably result in a loss of confidence of patients and HCPs into their healthcare system as ineffective medicines lead to treatment failure due to inadvertent suboptimal dosing (4). Moreover this contributes to a severe public health financial burden which mainly affects vulnerable patients (1). According to Fernandes et al. SSMs account for 7.8% of the net market value (111). Costs include payment for replacement therapy, additional drugs to cure the adverse effects or repeated courses, costs for lost

productivity in addition to increased direct healthcare costs as well as the necessity to develop new medicines against resistances (4). In order to break out of this circle, cooperation between the multiple national, regional and international stakeholders needs to be strengthened and intensified. Ideally a globally harmonised process system and guidelines are required (e.g. pharmacovigilance, quality testing), which are evidence-based and directed towards the detection, identification and removal SSMs from the market place- that is the only way that healthcare providers can jointly protect patients health worldwide.

6 Regulations and sanctions to prevent SSMs

The production and dissemination of each pharmaceutical product has to adhere to the principles of good clinical (GCP), manufacturing (GMP), distribution (GDP), pharmacovigilance practices (GVP) and guidelines of the International Conference on Harmonization (ICH) (122). These include post-marketing surveillance activities, regular inspection of manufacturers and the supply chain (wholesalers, distributors, retailers) by health authorities. QC testing as well as implementation of regulatory actions in the case of incompliance (123–125). A detailed specification for each of the approved medicinal products is set down in the marketing authorization (126).

SSMs mainly arise due to non-compliance with standards for GMP, GCP and GVP for centrally and nationally authorized products (127). They are the results of inadvertent manufacturing errors by legitimate manufacturers, negligent distribution practices of suppliers, human error or insufficient human and financial resources (128,129). In case of detection of SSMs, there are regulations in place for manufacturing authorization holders including measures such as the recall of defective batches of a medicinal product from the market. The authorization holder is required to notify the relevant Competent Authority of any defect or abnormal restriction that could result in a recall (130). Moreover the Committee for Medicinal Products for Human Use (CHMP) performs entire benefit risk assessments of medicines to ascertain whether the marketing authorizations for these medicines should be maintained, varied, suspended or withdrawn (131). There are countries in the world (e.g. Latin America, Africa, Middle East), mostly developing countries, where either guidelines on quality, safety and efficacy could potentially differ from FDA

and EMA guidelines or guidelines are not enforced which inevitably could allow easier proliferation of SSMs (106).

A subsidiary of Glaxo Smith-Kline, PLC (GSK) received a settlement of civil and criminal charges of 750 million $US in 2010 from the US Department of Justice (DOJ) regarding production and distribution of several SSMs between 2001 and 2005 (132). Reasons for the substandard nature of the medicinal products were microbial contamination, potential sub- therapeutic or toxic levels of API and product mix-ups (133). Likewise Ranbaxy USA Inc. had to pay 150 million $US for production and dissemination of certain adulterated medicines made at two of their manufacturing facilities in India (134).

Amir Attaran described that there are great variabilities considering sanctions for SSMs in different countries (135). In the Netherlands, manufacturing a substandard medicine for the second time in two years is a criminal act and will result to an imprisonment of maximum six months (135) whereas in India, imprisonment for ten years or for lifetime with high penalties are imposed when SSMs cause death (136).

If SSMs are produced with intentional deceit, denoted as falsified medicines according to the new WHO definition (82), different policies are in place such as the Directive on prevention of the entry into the legal supply chain of falsified medicinal products (colloquially known as the ¨Falsified Medicines Directive¨ (2011/62/EU) (137). This Directive aims to prevent falsified medicines entering the legitimate supply chain and reaching patients by introducing four measures which will come into force on 9th February 2019 in most of the European countries (122). These actions include placement of two safety features on the packaging; revision of GDP guideline by adding new responsibilities for wholesalers; appending written confirmation from regulatory authority of exporting country for all active substances manufactured outside the EU certifying "GMP and control of the manufacturing site are equivalent to those in the EU", (138) and application of an obligatory logo on the websites of legally operating online pharmacies and approved retailers in the EU (applicable since 1st July 2015) (90,137). "The effective enforcement of existing penalties is crucial in addressing the falsification of medicines, active substances and excipients." This is stated in Article 118a of Directice 2001/83/EC (90). In January 2018 a

qualitative assessment of the effectiveness of criminal and civil penalties as well as administrative sanctions for the falsification of medicines in 28 EU countries was performed. It was concluded that all participating countries applied prison sentences for the falsification of medicines (at least three years in 20 EU member states). Due to the scarcity of data “on incidents in the Member States” it was difficult to evaluate the efficacy of the penalties. But overall in about 50% of the Member States administrative sanctions “were rated as effective” to reduce the presence of falsified medicines in the legal supply chain”. For purchases of medicines from illegal online pharmacies, criminal penalties are more effective than administrative sanctions (90).

The most recent incident of deliberate manufacturing of SSMs affected many patients in Germany where a pharmacist manipulated the pharmaceutical preparation of more than 50,000 individual anticancer treatments including the supply of 30 clinical trials. “The pharmacist violated Germany`s medicinal products law in 61,980 cases between 2012 and 2016” (139). This case was discovered by careful investigation, that the pharmacist had purchased less material (range 20-80%) than he had invoiced from the health assurance providers. The financial damage to the insurance companies amount to 65 million $US over 59 months (139). Thus, he had manufactured oncology preparations with suboptimal dosing (140). The pharmacist was arrested on the 28. November 2016 (139).

7 Part 1: Detection of SSMs by applying statistical methods on adverse effects of medicinal products

Adverse effects of medicinal products represent the core component of Pharmacovigilance (PV) which is defined as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other medicinal product-related problem (141–143). In order to improve public health by enhanced safety monitoring of drugs, health authorities have implemented several pharmacovigilance databases (144) where AEs and suspected adverse reactions are being collected and can be accessed by the public (e.g. Vigibase®, FDA Adverse Event Reporting System).

Since 2011 there have been ongoing efforts by the WHO on pharmacovigilance database Vigibase® to identify SSMs with statistical analysis based on AE reports (31,145). However, a broad literature search has confirmed that currently there is no gold standard method available in pharmacovigilance for detection of SSMs.

Vigibase®

The WHO global individual cases safety report (ICSR) database Vigibase® was generated in 1968 and is maintained by the UMC on behalf of the WHO. ICSRs have been received at the UMC from over 125 national or regional pharmacovigilance systems. Currently this computerized pharmacovigilance database contains in excess of 16 million spontaneous reports, making this currently the biggest safety database worldwide. The advantage of using spontaneous reporting for continuous data collection are low maintenance costs, indication of reporting countries and broad coverage of population treated with a wide range of medicinal products (146).

The research presented in the following section “has augmented and extended previous work conducted by UMC (31,33). This study included all marketed medicines in Vigibase® based on the 24 MedDRA® terms indicative of product quality defects containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine.”(147)

The analysis of Vigibase® is documented in the following manuscript published in Drug Safety Journal on 28th January 2017 (DOI 10.007/s40264-016-0499-5) (147)**.**

8 Identification of substandard medicines via disproportionality analysis of individual case safety reports

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Abstract

Introduction

The distribution and use of SSMs is a public health concern worldwide. The detection of SSMs is currently limited to expensive large-scale assay techniques such as HPLC. Since 2013, the Pharmacovigilance Department at Novartis Pharma AG has been analyzing drug-associated AEs related to 'product quality issues' with the aim of detecting defective medicines using spontaneous reporting. The method of identifying SSMs with spontaneous reporting was pioneered by the Monitoring Medicines project in 2011.

Methods

This retrospective review was based on data from the WHO Global ICSR database VigiBase® collected from January 2001 to December 2014. We conducted three different stratification analyses using the MGPS algorithm through the Oracle Empirica data-mining software. In total, 24 PTs from the Medical Dictionary for Regulatory Activities (MedDRA®) were used to identify poor-quality medicines. To identify potential SSMs for further evaluation, a cutoff of 2.0 for EB05, the lower 95% interval of the EBGM was applied. We carried out a literature search for advisory letters related to defective medicinal products to validate our findings. Furthermore, we aimed to

assess whether we could confirm two SSMs first identified by the UMC with our stratification method.

Results

The analysis of ICSRs based on the specified selection criteria and threshold yielded 2506 hits including medicinal products with an excess of reports of product quality defects relative to other medicines in the database. Further investigations and a pilot study in five authorized medicinal products (proprietary and generic) licensed by a single marketing authorization holder, containing (valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine) were performed. This resulted in an output of 23 potential SSMs. The literature search identified two communications issued to health professionals concerning a substandard rivastigmine patch, which validated our initial findings. Furthermore, we identified excess reporting of product quality issues with an ethinyl estradiol/norgestrel combination and with salbutamol. These were categorized as confirmed clusters of SSFFC medical products by the UMC in 2014.

Conclusion

This study illustrates the value of data mining of spontaneous AE reports and the applicability of disproportionality analysis to identify potential SSMs.

Electronic supplementary material

The online version of this article (doi:10.1007/s40264-016-0499-5) contains supplementary material, which is available to authorized users.

Key Points

Application of an appropriate signal-detection method and careful analysis of spontaneous reporting systems supports the monitoring of quality defects and can identify SSMs.
Important challenges in the identification of SSMs include missing data from ICSRs as well as a lack of samples of suspected SSMs for verification testing, the latter being a direct result of the research being conducted retrospectively.

1. Introduction

By law, both innovative and generic medicines must be manufactured in accordance with regulatory requirements (148,149). A detailed specification for the finished product is set down in the marketing authorization (150). SSMs that do not conform with the specification—and therefore may compromise patient safety because of defects in the quantity of the active substance—may occur with both proprietary and generic medicines (4). The use of SSMs is a poorly researched public health concern worldwide (151,152). SSMs are not counterfeit, falsified, or fraudulent but are poor quality and represent a significant risk to patients. There is published evidence that the use of such medicines can result in treatment failure (12) or even death (153).

1.1. Challenges Underlying the Detection of SSMs

In total, 42 analytical technologies are available for identifying SSMs or falsified medicines, both devices for laboratory testing, such as the gold standard HPLC, and in-field testing devices such as Raman spectroscopy (26). The disadvantages of many laboratory testing devices are that they require laboratory facilities and highly trained personnel and that costs for these devices range from $US50,000 to 300,000. These instruments are not appropriate for routine product quality assessment in many of the low- and middle-income countries most affected by SSMs (26). Field devices are less expensive but also less sensitive. This study discusses an inexpensive and sustainable statistical detection method that can be applied in routine product quality assessments in all markets.

1.2. Spontaneous Reporting Systems

Spontaneous reporting systems represent the most common method of pharmacovigilance in the post marketing phase. They help generate hypotheses that could result in regulatory warning letters or changes to safety labels (154). Although it is generally not possible to establish absolute proof of failure to meet the authorized specification of a medicine from ICSRs in VigiBase® alone, as it is not possible to retrieve samples for confirmatory analysis testing, this data source can support the identification of hypotheses about potential poor-quality medicines associated with AEs (31,33).

The Monitoring Medicines project coordinated by UMC in 2011 demonstrated that spontaneous reporting could provide an indication of the presence of SSFFC medical products in healthcare

systems. The UMC developed a signal-detection method in a retrospective setting using 24 MedDRA® PTs indicative of inferior product quality within VigiBase®. A data-mining approach with three algorithms was applied to identify medicinal products associated with a higher-than-expected number of ICSRs. The main determinant was the lower 95% confidence interval (CI) of the comparative information component ICΔ exceeding 0. Several clusters of medicinal products with excess reporting of potential quality issues were highlighted and confirmed by information on product recalls or deficiencies. In 2014, UMC implemented the developed algorithms on national pharmacovigilance data. Some of the identified clusters of the suspected SSMs could be validated by national regulators. Limitations of the survey included late ICSR submissions to Vigibase® and lack of data quality (155).

This pilot study used a data-mining approach broadly analogous to that of the UMC Monitoring Medicines project, but we applied a different disproportionality algorithm to detect potential SSMs. We employed the three stratification strategies in the pilot study on all five active substances and compared the results, whereas the UMC Monitoring Medicines project used these data-mining approaches independently. The other main difference was that the Monitoring Medicines project focused on the detection of falsified medicines, whereas our study targeted the identification of potential SSMs.

1.3. Objectives

The primary objective was to evaluate whether disproportionality analysis applied to individual case reports, accompanied by statistical stratification techniques, could be used for the detection of potential SSMs. Furthermore, we aimed to validate these techniques by comparing the results against examples from the literature of known and previously evaluated cases of SSMs reported to Vigibase®.

2. Materials and Methods

2.1. Data Source

Vigibase® was selected as the basis for research to identify potential safety hazards associated with SSMs without identifying individual patients or the original source of the reports (156). We used the EB05 ratios produced by the Empirica Signal system, data-mining software (version 7.3.3.0.354, ORACLE) applied to ICSRs in VigiBase®.

2.2. Empirica Signal Application

Empirica Signal is a high-performance implementation of the MGPS algorithm, which is linked to the marketing authorization holder (MAH) safety database, Argus Safety. For a drug–event combination (DEC), the adjusted value of an observed/expected ratio is denoted as the EBGM value (157). The MGPS data-mining algorithm includes the computation of two-sided 90% CIs (EB05 < EB95) for EBGM. In general, MAHs and regulatory authorities use an EB05 or EBGM > 2 as a screening threshold for observations of disproportional reporting (ODRs) (158).

2.3. Data-Mining Analysis

We used 24 MedDRA® (version 17.0) PTs considered indicative of potential SSMs for the AE data-mining queries. The PTs were the same as those applied by the Monitoring Medicines project in 2011 (31). The 24 MedDRA terms used in this study analysis were as follows:

Drug ineffective; Therapeutic response unexpected; No therapeutic response; Therapeutic product ineffective; Therapeutic response unexpected with drug substitution; Therapeutic response decreased; Therapeutic response delayed; Product measured potency issue; Therapeutic response prolonged; Therapeutic response increased; Product quality issue; Drug effect increased; Product label issues; Unintended pregnancy; Physical product label issue; Product packaging quantity issue; Drug effect decreased; Product lot number issue; Product formulation issue; Drug effect delayed; Product barcode issue; Product identification number issue; Drug effect prolonged; Poor quality drug administered.

Three different stratification strategies for detecting potential cases of product defects were assessed:

1. Medicines with an excess number of reports on the selected PTs relative to all other products in Vigibase® in the specified timeframe.

2. Medicines with an excess number of reports on the selected PTs relative to other products containing the same active pharmaceutical ingredients.

3. Medicines with an excess number of reports on the selected PTs relative to other products containing the same pharmaceutical substances in a specific country and year.

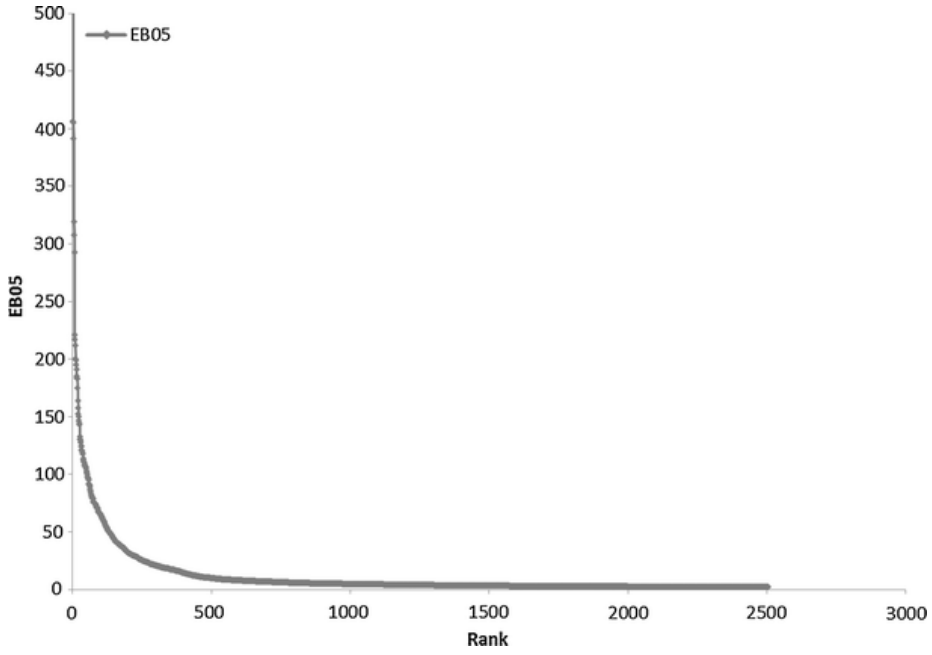
The third data-mining run was generated based on the stratification variables country and year of occurrence assuming the first and second data-mining runs showed an $EB05 \geq 2$.

We excluded all ICSRs that did not specify the name of the medicinal product ('NOS' [not otherwise specified] or generic names in VigiBase®) as the hit could refer to multiple trade names. To evaluate the statistical significance of the disproportional reporting ratios for each DEC, we analyzed reports of trade names with $N \geq 1$ ICSRs; $EBGM \geq 2$, and $EB05 \geq 2$ (157). N was a significant index for monitoring the emergence of an AE but was independent of the signal score (55).

The entire dataset within VigiBase® was systematically screened using the specified MedDRA® PTs for higher-than-expected DECs. Specific medicinal products with an $EB05 \geq 2$ (Figure 4) were evaluated further.

Figure 4 Excess reporting of medicinal products in Vigibase® based on selected MedDRA preferred terms (EB05 ≥ 2)

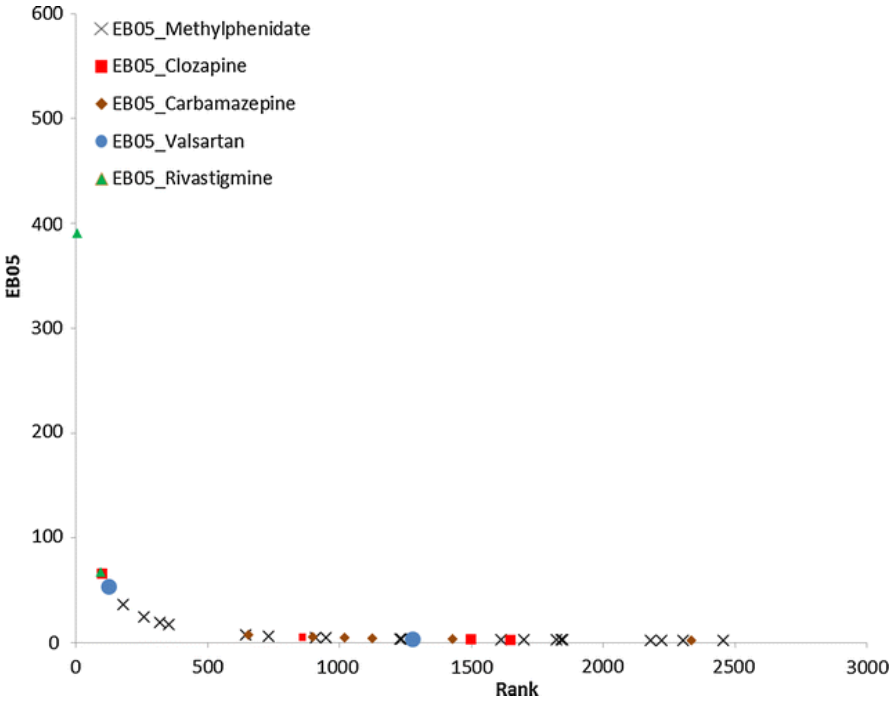
Output for all medicinal products (proprietary and generic as well as pharmaceuticals indicated by generic name or 'not otherwise specified') that were associated with a higher than expected number of individual case safety reports (EB05 ≥ 2), which warranted further investigation. EB05 fifth percentile of the confidence interval for the Empirical Bayes Geometric Mean



We then performed a pilot study on five medicinal products originally licensed by a single manufacturer but no longer patent protected: valsartan, methylphenidate, rivastigmine, clozapine, and carbamazepine (Figure 5).

Figure 5 Excess reporting in Vigibase® (EB05 ≥ 2) of 23 proprietary and generic marketed medicines containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine

EB05 fifth percentile of the confidence interval for the Empirical Bayes Geometric Mean



In the analysis of this pilot study, the results for the names of the generic medicines as well as the respective equivalent proprietary products containing the five active substances were further investigated, represented in Figs. 6, 7 and 8, and the corresponding EB05 values summarized in Table 2. Each of the figures demonstrates the excess reporting rates of one of the stratification strategies.

Figure 6 Excess reporting of generic forms and corresponding Novartis products of five selected active pharmaceutical ingredients

Fourteen pharmaceuticals with excess reporting rates (EB05 ≥ 2) via application of stratification strategy 1. Terms such as 'valsartan 1' refer to the 14 Novartis brand trade names and Novartis generic medicines identified in this study. Methylphenidate 1,4,5; carbamazepine 2, and rivastigmine 1 show reports with multiple MedDRA® terms. Novartis valsartan, rivastigmine, and clozapine are not included in this figure, as the reporting rates of these products did not meet the threshold (EB05 values <2). EB05 fifth percentile of the confidence interval for the Empirical Bayes Geometric Mean, N number of occurrences

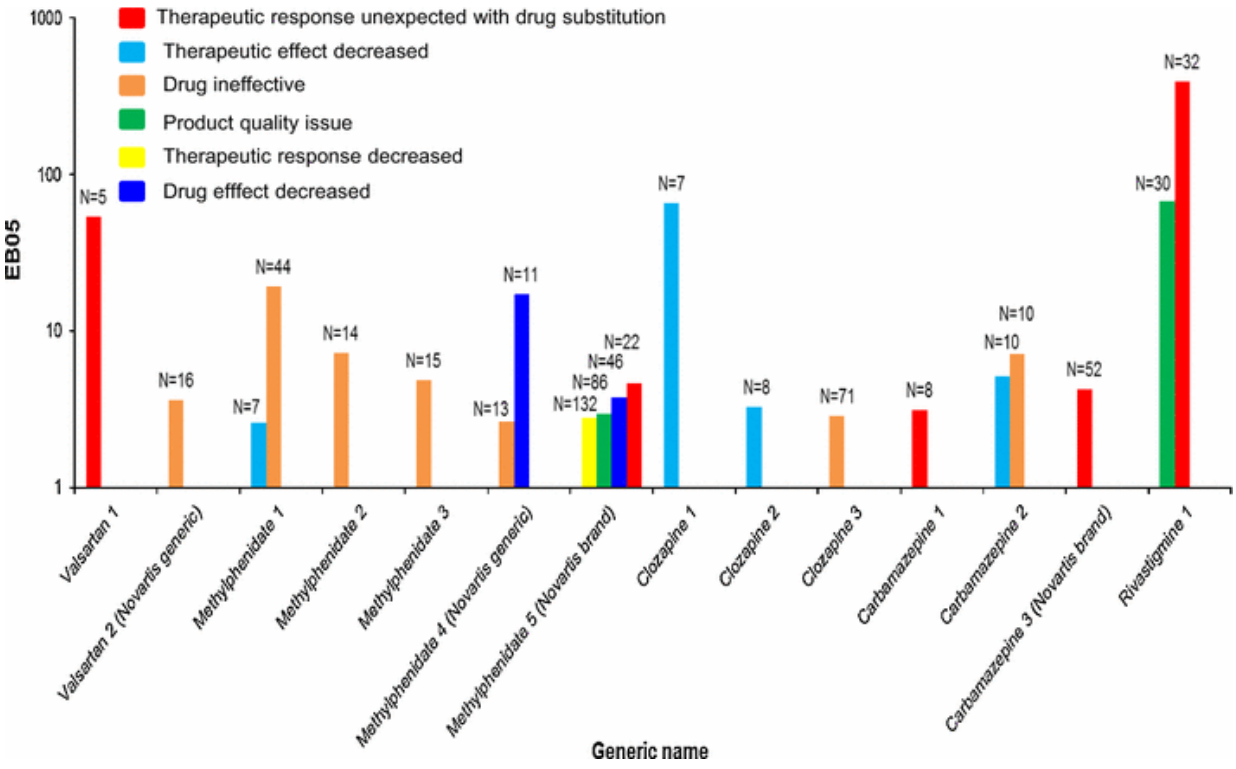


Figure 7 Assessment of excess reporting of generic forms and respective Novartis equivalent of selected active pharmaceutical ingredients with the same substance

Seven medicinal products with excess reporting rates (EB05 ≥ 2) via application of stratification strategy 2. The other seven medicinal products (Figure 6) revealed EB05 values < 2 or were not reported (see Table 2). The data on the y axis are shown in logarithmic form; EB05 fifth percentile of the confidence interval for the Empirical Bayes Geometric Mean, N number of occurrences

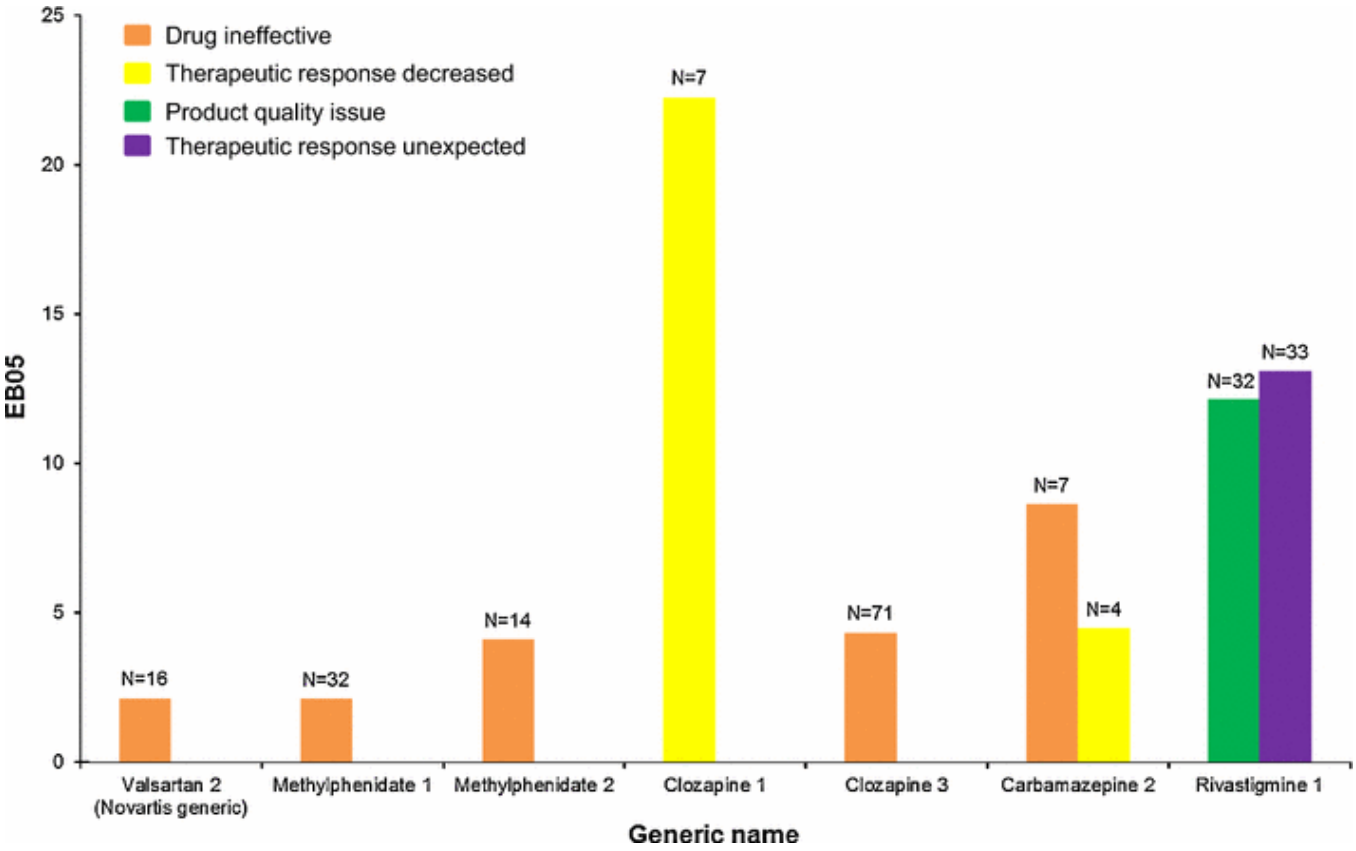


Figure 8 Country–year excess reporting of rivastigmine patch in 2 consecutive years

Multiple MedDRA® terms were reported for the same medicinal product; EB05 fifth percentile of the confidence interval for the Empirical Bayes Geometric Mean, N number of occurrences

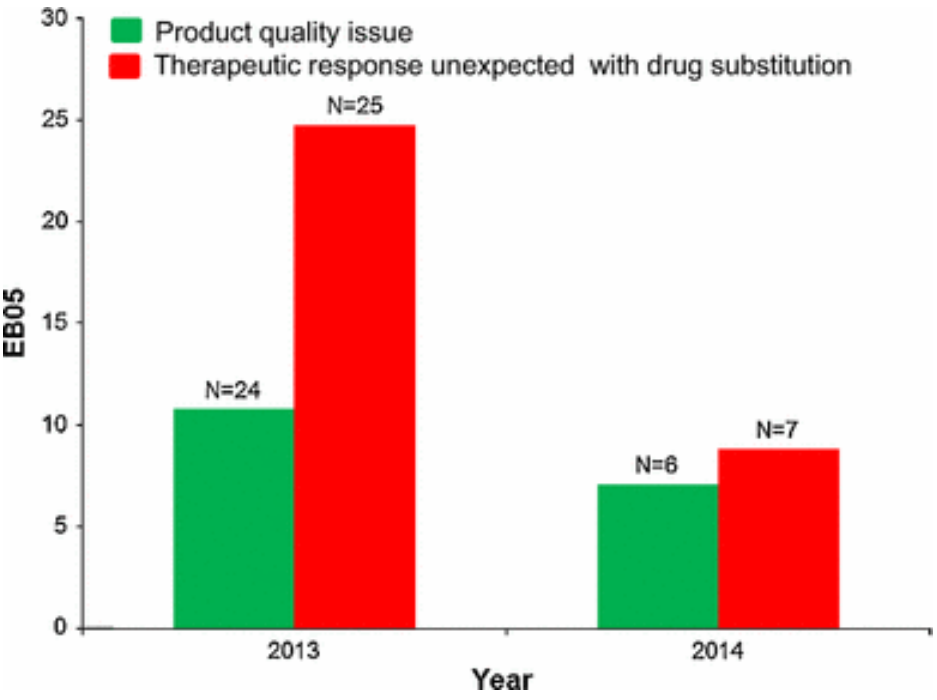


Table 2 Summary of identified trade names with excess reporting rates of the three stratification strategies on five active pharmaceutical ingredients

Summary of identified trade names with excess reporting rates of the three stratification strategies on five active pharmaceutical ingredients

Medicinal product	Drug formu-lation	Stratification strategy 1: Excess reporting rates (EB05) relative to other products in the database for 14-year study period[a]	Stratification strategy 2: Excess reporting rates (EB05) for pharmaceuticals with the same substance[a]	Stratification strategy 3: Country–year specific excess reporting rates (EB05)
Valsartan 1	Tablet	53.58	NR	ND
Valsartan 2	Tablet	3.62	2.128	Canada 2012: 0.23–0.99
Methyl-phenidate 1	Tablet	2.61–19.18	0.61–2.11	Canada 2001: 0.70–1.92 2010: 0.34–1.20 2011: 1.75
Methyl-phenidate 2	Tablet	7.21	4.094	South Africa 2004: 0.70 2005: 0.50 2011: 1.20
Methyl-phenidate 3	Tablet	4.85	0.6–1.49	ND
Methyl-phenidate 4	Tablet	2.6–17.2	1.14–4.40	Denmark 2005: 0.93–1.07
Methyl-phenidate 5	Tablet	2.8–3.8	0.24–0.84	ND

Summary of identified trade names with excess reporting rates of the three stratification strategies on five active pharmaceutical ingredients

Medicinal product	Drug formu-lation	Stratification strategy 1: Excess reporting rates (EB05) relative to other products in the database for 14-year study period[a]	Stratification strategy 2: Excess reporting rates (EB05) for pharmaceuticals with the same substance[a]	Stratification strategy 3: Country–year specific excess reporting rates (EB05)
Methyl-phenidate 6	Patch	2.15–36.51	0.3–1.53	ND
Methyl-phenidate 7	Tablet	5.08	0.13–0.77	ND
Methyl-phenidate 8	Tablet	3.75	0.07–0.97	ND
Methyl-phenidate 9	Tablet	2.63	0.05–1.13	ND
Methyl-phenidate 10	Tablet	2.22	0.02–1.60	ND
Methyl-phenidate 11	Tablet	2.03	0–0.68	ND
Clozapine 1	Tablet	65.77	22.275	Brazil, 2011: 1.42
Clozapine 2	Tablet	3.13	0.30–0.48	ND
Clozapine 3	Tablet	2.89	4.332	Canada 2010: 1.17 2011: 0.35 2012: 0.39 2013: 0.57

Summary of identified trade names with excess reporting rates of the three stratification strategies on five active pharmaceutical ingredients

Medicinal product	Drug formu-lation	Stratification strategy 1: Excess reporting rates (EB05) relative to other products in the database for 14-year study period[a]	Stratification strategy 2: Excess reporting rates (EB05) for pharmaceuticals with the same substance[a]	Stratification strategy 3: Country–year specific excess reporting rates (EB05)
Clozapine 4b	Tablet	5.30	4.32–15.0	Italy 2011: 0.49–0.75 2013: 0.25–1.5 2014: 0.92–9.06
Carbamazepine 1	Tablet	3.27	0.86	ND
Carbamazepine 2	Tablet	5.12–7.1	8.63–4.46	Canada 2003: 0.83 2012: 0.58
Carbamazepine 3	Tablet	4.21	0.68–0.78	ND
Carbamazepine 4b	Tablet	2.12–4.52	2.478	Italy 2011: 20.7 2012: 5.36 2013: 0.30–4.24 2014: 2.87 Mexico, 2014: 0.38
Carbamazepine 5	Tablet	4.12	[0.77-1.31]	ND
Rivastigmine 1	Patch	67.90–391.05	12.16–13.1	Netherlands 2013: 10.8–24.74 2014: 7.07–8.83

EB05: fifth percentile of the confidence interval for the empirical Bayes geometric mean

Summary of identified trade names with excess reporting rates of the three stratification strategies on five active pharmaceutical ingredients

Medicinal product	Drug formu-lation	Stratification strategy 1: Excess reporting rates (EB05) relative to other products in the database for 14-year study period[a]	Stratification strategy 2: Excess reporting rates (EB05) for pharmaceuticals with the same substance[a]	Stratification strategy 3: Country–year specific excess reporting rates (EB05)

INN international non-proprietary name, ND not done, NR not reported

[a] Ranges are used as there were reports of products with multiple MedDRA® terms. ND indicates that the country–year stratification was only generated when EB05 of stratification strategy 1 and 2 was ≥2

[b] Trade names could refer to INN name or to multiple generic brands

We performed a literature research for advisory letters and product or batch withdrawals for each of the identified proprietary and generic products through official health authority and national pharmacovigilance center websites (independent of the MAH or manufacturer) concentrating on product quality issues or defects. We did not conduct a systematic review of all publications, as the research for advisory letters published by independent researchers or by the competent authorities was deemed adequate for the purposes of this study. Search terms included combinations of the following keywords: advisory letter, drug removal, substandard, quality, and trade name with country of occurrence of potential SSMs from retrospective analysis. Searches were limited to publications after 2001. The keywords were applied to the following websites: US FDA, MHRA, EMA, and selected pharmacovigilance center websites, e.g., Netherlands Pharmacovigilance Centre. From the resulting alerts, we extracted the product name, dosage form, year of the alert, and description of the product defect (4,159–161). In addition to the literature research, we applied the three stratification strategies to two confirmed SSMs categorized by UMC in 2014 as confirmed SSFFC clusters (33).

3. Results

Based on the search strategy and threshold criteria described, 2506 DECs were generated (see Figure 4). We excluded 664 potential target SSMs from further analysis, as the precise trade name of the product was not specified. The 664 excluded hits contained 478 medicinal products denoted as NOS, and 186 reports using generic names (e.g., fluoxetine) or broad therapeutic categories or drug class (e.g., 'protectives against ultraviolet radiation for topical use' or 'centrally acting sympathomimetics'). The excluded hits could not be associated with a particular proprietary medicine or with a specific manufacturer if the product was a generic. Thus, warning letters were not applicable, as they always involved a specific medicinal product.

In total, 23 trade names of generic and proprietary medicinal products resulted when we filtered the data to include only reports associated with pharmaceuticals containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine (Figure 5). Table 2 shows the stratification strategy results (EB05 values) of 23 proprietary and generic marketed medicines containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine. Excess reporting for both stratification method 1 and 2 was determined for nine medicinal products, whereas three pharmaceuticals (clozapine 4, carbamazepine 4, and rivastigmine 1) showed high EB05 values for all three data-mining operations. The three products with potential quality defects identified originated in Italy and the Netherlands.

In a subset analysis, we filtered the trade names of generic medicines produced by Novartis and the equivalent proprietary medicines containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine. This resulted in 21 ODRs involving 14 proprietary medicines, as occasionally there were reports of products with multiple MedDRA® terms (Figure 6, Figure 7).

The results of the stratification analysis are shown in Figure 6, Figure 7 and Figure 8. Figure 6 shows excess reporting rates for all generic forms, including Novartis' own generic products, valsartan and methylphenidate. The reporting rates of Novartis valsartan, rivastigmine, and clozapine did not meet the threshold (EB05 values <2) and are therefore not included in this

figure. In analogy to Figure 6, Figure 7 illustrates excess reporting rates of 7 of 14 medicinal products, as the EB05 value of the other seven pharmaceuticals for product substance stratification did not meet the threshold (EB05 <2).) The criterion for excess reporting for stratification analysis 1 and 2 was fulfilled for seven medicinal products, whereas the rivastigmine patch met all the criteria, including the country–year stratification operation (Figure 8).

The literature search for the rivastigmine patch revealed two letters relating to quality defects and associated safety concerns (159,160). Details of ICSRs provided in direct health professional communications could be matched with specific case descriptions provided in the VigiBase® records, including PT, country, and year of occurrence (Figure 6). This medicinal product showed the highest value of EBGM and EB05 score with PT "Therapeutic response unexpected with drug substitution" (EBGM = 528,689; EB05 = 391,054; N = 32) compared with other compounds under study (Figure 7). It was evident from Vigibase® and the published 'dear healthcare provider letters' that a case series had been identified. The literature research for advisory letters for the other two pharmaceuticals (clozapine 4, carbamazepine 4), which also met all three stratification criteria was impeded because the identified proprietary names could refer to the international non-proprietary name (INN) or to multiple generic brands. No advisory letter on safety or quality was found for the other medicinal products under study.

Two medicinal products, salbutamol and ethinyl estradiol/norgestrel combination tablets, were identified as confirmed SSFFC clusters by UMC in 2014 because of excess reporting rates. The ethinyl estradiol/norgestrel tablets were referenced in an FDA warning letter in 2012 about a recall of 14 batches because of the possibility of inexact tablet counts or "out of sequence" tablets (162). In our study, this medicinal product showed ODRs that exceeded thresholds for stratification strategies 1 and 3. In 2012, eight reports in the USA of "product quality issue" with an EB05 value of 26.77 for this combination product were submitted to Vigibase®.

Quality defects, including lack of effect due to inadequate administration technique and use of expired products, were documented with a salbutamol solution in the USA in 2012 (33). In this report, the medicinal product showed ODRs that exceeded the thresholds for stratification strategies 1 and 3. There were 96 reports of 'drug ineffective' (EB05 4.5); 102 cases of 'product quality issue' (EB05 20.28), and nine reports of 'therapeutic response decreased' (EB05 2.04) submitted to Vigibase®. The stratification results for both products are presented in Table 3 (33).

Table 3 Summary of pharmaceuticals with excess reporting for all three stratification strategies for two confirmed substandard products

Summary of pharmaceuticals with excess reporting for all three stratification strategies for two confirmed substandard products (55)

Medicinal product	**Drug formulation**	**Excess reporting rates (EB05) relative to other products in the database for 14-year study period[a]**	**Excess reporting rates (EB05) from the product substance stratification analysis**	**Excess reporting rates (EB05) from the country year stratification analysis**
Ethinyl estradiol and norgestrel	Tablet	4.87–174.77	0.32–0.54	USA, 2012: 0.3–26.7
Salbutamol	Tablet	2.10–16.14	0.039–1.21	USA, 2012: 0.13–4.5

[a]Ranges are used as there were reports of products with multiple MedDRA® terms

4. Discussion

Our study presents a new and effective way to detect potential SSMs. The data-mining approach used in this pilot study resembled the method presented in the UMC Monitoring Medicines project (31), but we applied a different disproportionality algorithm to detect

potential SSMs. In the first sub-analysis, we identified active substances where reporting for selected PTs exceeded the threshold when compared with all other medicinal products in Vigibase®, whereas the Monitoring Medicines project started by selecting active substances within a particular country. Our second step was to evaluate disproportionality results for products containing the same active substance. Finally, for each medicinal product where reporting above the threshold occurred, we identified the country and year of occurrence. The UMC group analyzed the top 30 medicinal products with the highest disproportionality scores and assessed a further randomly selected dataset for comparison, whereas we analyzed the entire dataset for five active substances selected as the basis for this research and applied all stratification strategies on these five active substances and compared the results. The application of the three data-mining stratification strategies on ICSRs using the Empirica software discovered medicinal products with quality defects that were then confirmed by advisory letters from official health authority and pharmacovigilance centers. VigiBase® proved to be useful reference point for the identification of clusters of potential defective medicines.

The research presented here has augmented and extended previous work conducted by UMC (31,33). This study included all marketed medicines in Vigibase® based on the 24 MedDRA® terms indicative of product quality defects containing valsartan, methylphenidate, rivastigmine, clozapine, or carbamazepine. Table 2 and Table 3 illustrate that there were excess reporting rates (EB05 $\geq$ 2) for both proprietary and generic medicines.

After extensive investigation of the 23 identified trade names with excess reporting rates in Vigibase®, one potential SSM fulfilled the criteria for all stratification strategies, and a product defect was confirmed via an independent report from the Pharmacovigilance Centre in the Netherlands (163) via distribution of two letters to healthcare professionals. In Figure 4, Figure 5, Figure 6, Figure 7, Figure 8 and Table 2, the ODRs for the rivastigmine patch demonstrated high EB05 values and were demonstrable outliers. Similar to rivastigmine 1, the other two pharmaceuticals clozapine 4 and carbamazepine 4 also met the EB05 threshold for all three stratification techniques, but the literature research for advisory letters was hampered by the absence of specific product details.

The identified excess reporting rates for two of three stratification strategies on confirmed substandard clusters of salbutamol and ethinyl estradiol/norgestrel reinforces the potential utility of this data-mining approach. Compared with detection of SSMs with analytical devices, this technique is a non-destructive and reproducible method that can support non-governmental centers, healthcare professionals, manufacturers, and health authorities in low- and middle-income countries to triage for confirmatory analysis testing of medicinal products.

The findings in this study support the need for further research to refine the algorithm so this exploratory research becomes a matter of routine programming within the competent authorities and MAHs. It is our intention to optimize the sensitivity and selectivity of the method described. It is clear from this initial study that public health benefits could result from the early detection and reporting of quality defects associated with SSMs.

We recognize there are limitations applicable to this systematic analysis for the detection of SSMs. Safety data collected by MAHs include reports of product complaints related to quality defects. According to the existing regulations, these two datasets (safety and quality) are governed rather differently, with quality under GMP and safety under Good Pharmacovigilance Practice (GPvP). There are multiple areas of overlap between safety and quality defects. For example, there is significant duplication across aggregate safety reports and submission of these data within periodic quality reports. Nevertheless, there are gaps in the analyses of these data in combination in order to form potentially important conclusions that may impact public health. An illustration of this is provided in Figure 9. Manufacturers take great care to reconcile the two datasets according to the regulations. Regulatory inspections often focus on this area, and this has resulted in findings (164), warning letters (165), and more serious sanctions (166).

Our recommendation is that both regulatory authorities and MAHs could consider the following.

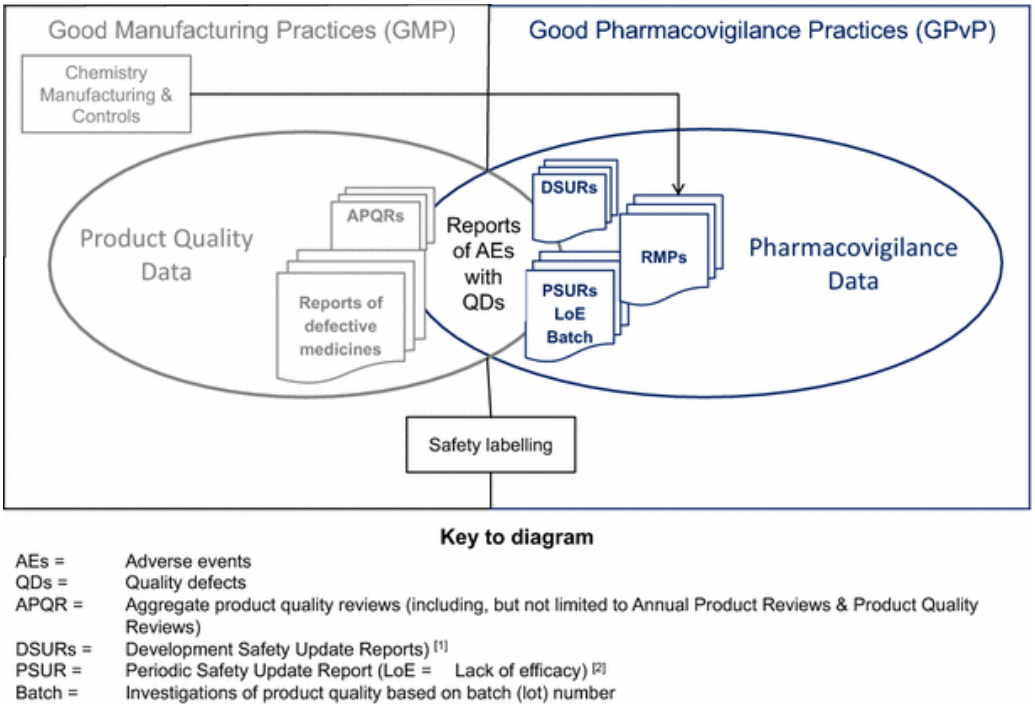
- Application of this method to all medicines using large safety databases (e.g.,

EudraVigilance) to aid the detection of adverse patient outcomes related to suspected SSMs. The results could help improve public health by earlier identification of products with quality defects.

- Recommend targeted analytical testing in developing countries or regions based on the results of disproportionality analyses to detect SSMs.

Figure 9 Inter-relationships of good manufacturing practices and good pharmacovigilance practices, and aggregate regulatory reports

AE adverse event, *APQR* aggregate product quality reviews (including but not limited to annual product reviews and product quality reviews), *DSUR* development safety update reports (167), *LoE* lack of efficacy (168), *QD* quality defects, *PSUR* periodic safety update report, *RMP* risk management plan



Juhlin et al. (33) faced the same challenges during their survey. This was a retrospective study, therefore we have not been able to obtain samples of the suspected SSMs for testing as they were no longer available. In Vigibase®, the sensitive personal health information of patients and the contact details for patients and primary reporters are anonymized to prevent the

identification of individuals (169). Consequently, it was not possible to contact the report sources to obtain follow-up data and thereby consolidate and potentially extend our preliminary findings. In addition, the majority of drugs in VigiBase® were described by their APIs in a non-specific manner as NOS.

Under-reporting (170), particularly by resource-limited countries, meant only a relatively small number of ICSRs were associated with lack of efficacy events. Most of the ICSRs in this study originated from Europe (Italy, Netherlands, Denmark) and from Canada. Relatively few ICSRs originated from Brazil, Mexico, or South Africa. Healthcare professionals play a very important role in spontaneous reporting and, particularly in Europe, patient reporting has been actively promoted (170). This could be augmented by requesting that patients and caregivers take action to report possible quality defects and lack of efficacy.

We determined there was no international consensus regarding MedDRA® terms describing SSMs. Initially, we started with the 24 PTs (31). In contrast, the UMC publication from 2014 (33) included 77 PTs. We propose that the pharmaceutical industry and regulatory authorities collaborate with the MedDRA® Maintenance and Support Services Organization (MSSO) to develop a standardized MedDRA® query (SMQ) for SSMs. Perhaps the most important adjunct to the research described is the essential activity of conducting field-based sampling and testing. New portable devices will allow rapid and accurate assessment of samples purchased from suppliers to further assess the viability of signals generated from the screening of VigiBase®.

5. Conclusions

We have provided evidence of an effective method for the detection of SSM signals using a large pharmacovigilance dataset. The signal that was generated from the rivastigmine patch was confirmed by two independent publications in the Netherlands, both of which emanated from a pharmacist-based monitoring program (159,160). Furthermore, we confirmed the results of the data-mining technique that the ODRs for two medicinal products were related to SSMs as originally shown by UMC. Our findings, using this novel method of detecting

potential SSMs, are a positive step towards addressing the supply of poor-quality medicines. Further validation would enable the routine use of this approach by competent authorities and MAHs.

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Compliance with Ethical Standards

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No specific funding was received for this study.

Conflicts of interest

Zahra Anita Trippe, Bruno Brendani, and David Lewis are employed by Novartis Pharma AG. Christoph Meier has no conflicts of interest.

9 Part 2: Analytical tools for detection of SSMs

Part II describes the main analytical devices currently used for the detection of SSMs. The focus will be on the PharmaChk technology, a portable screening instrument which allows accurate quantitative assessment of API. Thus, we set up a formal collaboration between Novartis Pharma AG, Basel and Professor Muhammad Zaman from the Biomechanical Engineering Department of Boston University and initiated the assay development of the essential antimalarial drug Coartem® on this device.

Most of the time, "…low-quality medications are only detected after they harm enough patients to alert medical caregivers…" (171). Hence it is difficult to identify SSMs (172) before they cause any harm. The complex medicine supply system and the absence of a worldwide standardized tracking system demands large-scale assay techniques to analyze the chemical composition of medicinal products (172).

The detection of SSMs is currently limited to analytical technologies (147). The majority of published research articles on detection of poor quality medicines with analytical technologies comprise both falsified *and* SSMs. While authentication assessments are well suited to identify falsified medicines, the evaluation of pharmaceutical content, impurities, degradation products (173) and dissolution profile is substantial for reliably detecting SSMs (28,173).

Routine quality testing of medicines applying pharmacopoeial analysis is costly and requires sophisticated equipment (27). "Pharmacopoeial requirements in countries form part of national legislation, defining the specifications" and standards "which pharmaceutical products circulating on their market must fulfil" (174) to deliver high quality medicines (175). According to a recent study, as an example, the average price offered for the analysis of a single medicine sample to control product quality by a WHO-prequalified laboratory in South Africa was 1,580 $US (27) which is higher than the average monthly gross wage in South Africa (1486.19 $US in Q1 1018 (176). Performing systematical drug screenings would therefore be a substantial cost driver. To protect patients globally from the use of SSMs, there is increased need for innovative field-

applicable technologies to adequately detect low quality medicines as soon as they appear on the market (26,173,177,178).

9.1 Analytical technologies for medicine quality evaluation

Medicine quality analytical technologies is based on the following four (essential) key pillars:

- Verification of API identity
- Determination of API content
- Assessment of disintegration of the pharmaceutical formulation
- Demonstration of dissolution of the medicine in the human body (bioavailability) (179,180)

Generally, analytical technologies can be characterized in field and laboratory devices using a) destructive and b) non-destructive methods "to ensure the identity, strength, quality, purity and potency of the" (181) medicinal product. Field devices are portable and rather simple to use in remote areas (182) whilst laboratory instruments are cumbersome, require trained personnel and sophisticated devices (179). Most of the laboratory devices use destructive methods and do not maintain the integrity of the pharmaceutical formulation whereas screening devices [e.g. handheld Raman spectrometer, NIR spectrometer] allow measurements of tablets or capsules within their blister packaging (183,184). To date, a range of various analytical instruments are required for the assessment of medicines quality according to the four pillars described above (53). The following analytical tools represent current conventional confirmatory and screening methods (185) that are globally used for quality evaluation of pharmaceuticals.

9.1.1 Confirmatory technologies

The purpose of medicine quality testing can be either for screening or for confirmatory assessment (186). Confirmatory technologies including HPLC, mass spectrometer (MS) and dissolution apparatus are costly, complex and require cumbersome repair and maintenance process. Consequently, there is a lack of quality assurance laboratories in developing countries. However,

these powerful laboratory instruments cannot be replaced by presumptive techniques such as Raman and NIR spectrometry as confirmatory technologies conclusively elucidate API's identity, quantity and release (179).

Table 4 Confirmatory laboratory technologies for quality of medicines evaluation

NAME	**DESCRIPTION**	**VARIATIONS**	**ADVANTAGES**	**DISADVANTAGES**
*HPLC	Separation technique that involves a solid stationary phase and a liquid mobile phase. „Separation of the components of a solution results from the difference in the relative distribution ratios of the solutes between the two phases.“ (187)	-HPLC-MS -Ultra-performance liquid chromatography (UPLC) -Reverse-phase liquid chromatography (RP-LC)	-High sensitivity (188) -Precise content determination	-Non-portable (189) -Cumbersome maintenance (189) -High instrumentation costs (190) -Qualified staff needs to prepare the samples in a well-equipped laboratory requiring delicate solvents and reagents (188)
*Gas chromatography (GC)	Separation technique that involves a solid stationary phase which is a high boiling point liquid coating absorbed on the surface of a granular solid in a column and a mobile phase which is an inert gas (187,191).	-GC coupled to a flame ionization detector (GC-FID) -GC-MS		
*Mass spectrometry (MS)	„MS utilizes the degree of deflection of charged particles by a magnetic field to find the relative masses of molecular ions and fragments“ (192)	-Direct analysis in real time (DART) -Desorption electrospray ionization (DESI)		

NAME	DESCRIPTION	VARIATIONS	ADVANTAGES	DISADVANTAGES
Ultraviolet (UV) spectrometry	UV spectrometry "involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution" (193). This method is used to characterize the chemical composition of medicine samples, confirms the identification of a substance through comparison with a reference spectrum (194) and evaluates the purity of medicine samples (195)	-HPLC-UV -CE-UV	-Simple and fast and reveals a moderate specificity (193)	-Not portable -Requires experienced personnel (53)
Capillary electrophoresis (CE)	Separation technique that separates molecules in an electric field according to size and charge. This technique is performed in a capillary that is filled with an electrolyte solution (196). CE technology can be applied for qualitative and quantitative determination of medicine samples (53)	CE-UV	-Requires only little training -Cheap analysis cost (53)	-Relies on a high electric field (issue in emerging countries) (53)
[+]Disintegration	The disintegration apparatus determines whether solid formulations "disintegrate within the prescribed time when placed in a liquid medium" (187)	/	Both tools are easy to operate and robust (197)	-Fixed volume of medium aggravates testing of poorly soluble medicines (198)
[+]Dissolution	The dissolution apparatus, "used as bioavailability indicator" (101) routinely performs QC tests (199,200) to "determine the amount of API(s) released from solid dosage forms, using a known volume of dissolution medium within a predetermined length of time (201). This analytical test represents a conclusive assessment as it can identify SSMs including the declared	Paddle and basket dissolution		-Simulation of gastrointestinal transit conditions is not easily possible with current dissolution techniques (197)

NAME	DESCRIPTION	VARIATIONS	ADVANTAGES	DISADVANTAGES
	API content (202) but altered dissolution profile (14)			

*Gold standard for verification, purity, quantification of many pharmaceutical substances (22,192, 217). + Physical analysis tests (101) including dissolution or disintegration test requirements are critical (204) for the characterization of the quality and performance of medicinal products (205).

9.1.2 Screening technologies

Qualitative and/or quantitative technologies" (206) (e.g. Raman spectrometry, TLC Minilab®) allow rapid analysis (207) of large volumes of pharmaceuticals "for preliminary identification of suspect medical products in the field" (206) but bear the risk of false positives (207). "They can only establish the possibility that a particular pharmaceutical compound is present…" (207). Hence, instruments (such as Raman or NIR spectrometer) can be effectively applied to narrow down the number of medicinal samples that will undergo confirmatory testing. In low and middle-income countries (LMIC) these instruments constitute the initial step of medicine quality assessment (179).

Table 5 Screening technologies for medicine quality assessment

NAME	DESCRIPTION	ADVANTAGES	DISADVANTAGES
Visual inspection	Visual inspection (printing, embossing, shape, odor, taste, consistency) represents the first (14) step for required medicines quality evaluation (173,185)	-Cheap -Can be used in-field setting	-Due to the lack of sensitivity and specificity (14) performing this analysis alone" (101) is not adequate to assess drug quality (173)
Handheld refractometer	Handheld refractometer can be used to measure the refractive index which determines the purity of liquids and solid substances. It further serves to quantify some APIs (173)	-Allows rapid analysis -Ease of use -Relatively low cost (208)	-Dispersion (seen as blurring and coloring of the border-line -Limited accuracy and precision due to the size and optical arrangement. -No control over the

NAME	DESCRIPTION	ADVANTAGES	DISADVANTAGES
			sample temperature (209)
Counterfeit Detection Device #3 (CD3)	This device evaluates the packaging material (primary and secondary packaging, and labelling) and packaging print. The dosage units (tablets, powders) are visually examined at specific wavelengths of light to determine if the observed images are consistent or not consistent with the library images of the authentic medicinal products which is pass or fail (185,210).	-Relatively cheap -Very effective in identifying differences in strength of a given product and the capability to identify SSMs (185)	-„Results are user dependent" -Can only compare to the images it owns in the library otherwise there is no analysis possible (185)
Thin layer chromato-graphy (TLC)	TLC is a semi quantitative separation technique. The stationary phase is a polar absorbent, usually finely ground alumina or silica particles. This absorbent. Since different substances are moving up the Thin-Layer Chromatography plate at different rates, they can be separated, identified and analyzed (211–213).	-Relatively cheap (179) -Simple (214)	-Cannot assess the exact amount of API content of medicine samples (101)
TLC Minilab®	Gold standard field-based screening technique (215) performs semi-quantitative TLC and disintegration testing to assess the identity, release and estimate the concentration of APIs (26,216,217)	-Portable (183) -Affordable -Acquires high samples throughput (218)	-"Competent, well trained users are required to obtain reliable results" (185) In addition, as this instrument applies a semi-quantitative method, it can reliably identify only grossly SSMs and should therefore not be used as an independent testing resource (218)
Paper chromato-graphy test card	Qualitative method which is designed to identify the API(s) as well as binders and fillers used in tablets and capsules such as chalk, talc and starch (219). "The test card consists of 12 lanes containing different reagents. The reactions of the reagents with the rising water in each lane generate colors to form a "color bar code" which can be analyzed visually by comparison with standard outcomes.	-Inexpensive -Fast analysis (219)	-Poor quantification of the API(s) -Due to the low specifity of this assay, false-positive results may be obtained (53)
[a]NIR spectrometry	Fingerprinting identity test measures the Raman or NIR spectra of the medicinal sample and	-High accuracy (177)	-Not quantitative results

NAME	DESCRIPTION	ADVANTAGES	DISADVANTAGES
[a]Raman	compare it to the respective reference spectrum in the library" (183,185)	-Nondestructive methods -Requires no sample preparation for testing a high throughput of medicinal samples (177) [analysis time 30 seconds] which appears as Fail/Pass results on the display of these instruments	-Relatively high instrumentation cost (183,185) -Inadequate for detecting SSMs (185,220,221)
[a] Nuclear magnetic resonance spectroscopy (NMR)	NMR spectroscopy detects the chemical environment of atomic nuclei by the absorption of radio-frequency electromagnetic radiation when in the presence of a high magnetic field (222)	-Quantitative analysis -Not destructive (223)	-Requires presence of high-magnetic-field environment - Very high instrumentation costs (224)

[a] Spectrometer techniques determine the overall composition of a drug product" (183,204)

9.1.2.1 Quantitative screening device under development

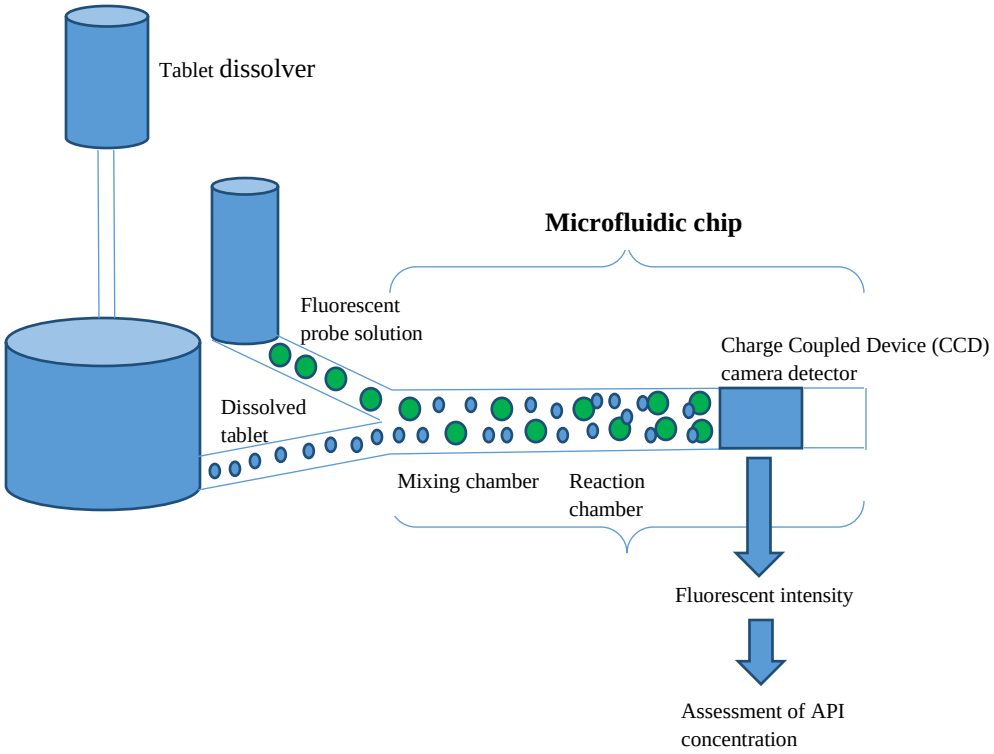
All screening tools described above mainly perform qualitative and semi-quantitative analysis of medicinal samples (225) (22). Currently the TLC Minilab® (Table 5) is the gold standard screening device for medicines quality evaluation and highly eligible for detecting falsified pharmaceuticals (215). Indeed the detection of SSMs requires the evaluation of pharmaceutical content, impurities, degradation products (173) and dissolution profile (28,173) . Presently, "no existing field technology is capable of reliable API quantification and kinetic release analysis" (215). Nevertheless, since 2014 there have been efforts from the Biomechanical Engineering department of BU to develop a portable screening technology (226), PharmaChk, which combines the attributes of assessing the exact API dosage and the dissolution profile of solid and liquid formulations (215).

The PharmaChk device is a field-based quality screening tool (215) with a high specificity enabling a fast quantitative assessment of drug ingredients (225). This instrument combines a

fluorescent or luminescent assay and microfluidic technology (29). Before being able to assess the API content of a medicinal sample, the PharmaChk instrument needs to be calibrated for the API of interest.

The determination of API concentration using the PharmaChk device is as follows (Figure 10): The tablet is dissolved in the tablet dissolver and is then pumped into the microfluidic chip where it is mixed with the fluorescent probe solution (29). The interaction of a specific probe with the API of interest in the reaction chamber generates a luminescent signal, that is captured by the charge coupled device (CCD) camera, and which reflects the quantity of the API of interest (29,189).

Figure 10 Assessment of API concentration using the PharmaChk instrument (29)



The PharmaChk screening instrument has several advantages. It accurately and specifically determines the content of the stated API(s) (in percentage) as well as the kinetic release (dissolution profile) of liquid and solid formulations (29,215,225). It further allows a relatively high throughput of samples, as the turnaround time for analysis of 1 sample amounts to 15 minutes

(171,225,227). This device "holds promise as a user-friendly, affordable (price estimate ~1,000 $US) and portable (~10-12 lbs suitcase) instrument for a quick evaluation of quality of medicines that can be used in the field. Pilot studies in Ghana and several locations in Asia have shown comparable results to gold standard HPLC (within 5%) (225). Limitations of the PharmaChk device are a) that the medicinal sample is destroyed under investigation and b) reagents are required for sample preparation (173). Due to the high specificity of PharmaChk technology, the probe and reference samples are necessary for every compound that will be tested. At present, assays for precise quantification of tetracycline and artesunate have been developed. Thus the development of an on-board reference database to facilitate high-throughput field testing of a broad variety of pharmaceuticals is required (228). According to Prof. Zaman, in the near future this instrument will also allow the quantification of excipients impurities and/or degradation products (229) for drugs of interest and therefore represent a well-suited screening device for reliably identifying SSMs.

After describing the relevant screening and confirmatory technologies commonly used for assessing medicines quality, in the next section there is focus on the use of the above mentioned devices to specifically identify SSMs.

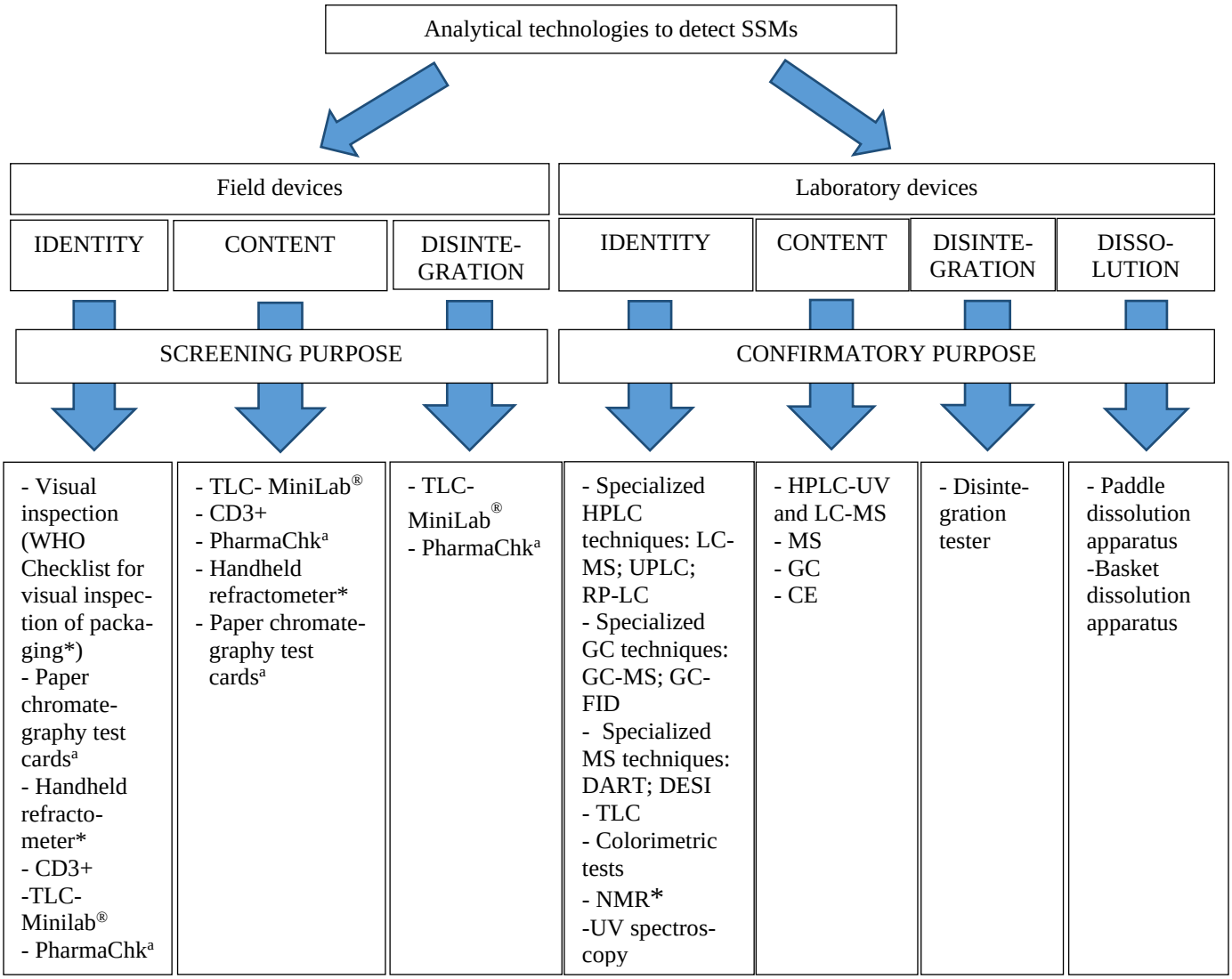
9.2 Suggested analytical technologies for detection of SSMs

The review article of Kovacs et al. (26) reported the availability of 42 unique technologies in 2014 on detection of falsified and SSMs. In order to classify substandard and falsified medicines, the Counterfeit Drug Forensic Investigation Network (CODFIN) (230) developed a systematic analytical workflow which has been used by several research groups to investigate malarial drug quality in developing countries (173). To evaluate the presence and content of the API (26), this workflow suggests packaging inspection, followed by colorimetric testing, spectroscopic methods including Raman and NIR and quantitative HPLC. For further determination of the substandard nature of a medicinal product, dissolution testing to determine the bioavailability as well as MS analysis to identify the sample ingredients, are envisaged. To identify the geographic source of the manufacturing site in confirmed cases of falsified medicines, analysis on elemental composition (profile of trace metals (183) with XRF, identification of excipients by isotope ratio MS (IRMS), X-ray diffraction (XRD) and NMR can be conducted (26).

In August 2017 the WHO published a draft guidance document on testing of “suspect” falsified medicines (231), however there is no guidance document on using analytical instrument for identifying SSMs. This working document describes the workflow on laboratory analysis of medicinal samples and presents examples of analytical techniques that may be used for package identification, screening and testing of suspected SSFFC products. In addition detailed guidance is provided concerning sampling of medicinal products and reporting of testing results. At the very beginning of this document “suspect” medicines are classified in three categories: The first category represents substandard medicines, the second unregistered/unlicensed medicines and the third category are falsified medicines. The guidance document clearly states that it focuses particularly on medicinal products of the third category, the falsified medicines (231). In the workflow description on laboratory analysis, only packaging analysis, including Raman or Fourier-transform infrared spectroscopy are used as screening technologies for medicines quality testing.

Based on literature research in the field of defective medicines, the following figure intends to present the most commonly used analytical technologies for the detection of SSMs (182). In addition¸ [Figure 11] includes the screening instruments which are currently under development.

Figure 11 Overview on currently and commonly used analytical methods for detection of SSMs



* Non-invasive methods. All other presented laboratory and field devices use invasive methods.

[a] Analytical technologies under development

9.3 **Discussion**

Analytical technologies for the assessment of quality of medicines is a fast moving field (26). The workflow developed by CODFIN (230) represents a first useful approach on identifying SSMs with analytical instruments. Other existing guidelines such as "WHO draft guidance on testing of "suspect" falsified medicines" (231) and the "Council of Europe: Testing of counterfeit/illegal

medicines" (232) clearly specifically deal with identifying falsified medicines and do not include SSMs. Notwithstanding, inclusion of to date field screening technologies in the CODFIN workflow is necessary. Relating to detection of SSMs, the PharmaChk device would be an essential add-on as quantitative screening instrument along with the existing qualitative screening devices Raman and NIR spectrometer in order to obtain a comprehensive picture of collected substandard medicine samples (233). In order to implement its worldwide application as a global standard (routine) workflow for medicines quality surveillance programs, further validation of these workflows is required. Before designating PharmaChk as a quantitative screening tool in the CODFIN workflow, more field studies need to be conducted.

Current variety of screening and confirmatory techniques allow post market surveillance and help to decrease the prevalence of poor-quality pharmaceuticals in the global supply chain (171). However, no ideal device has yet been identified to provide reliable results on identification, quantification, disintegration and dissolution profile of SSMs and fulfilling a range of desired criteria :

- Sturdy and durable (173)
- Low-cost (affordable)
- Easy-to-use (not requiring specific training)
- Sustainable (particular in hot and humid climates)
- Easy portability
- No sample preparation (no reagents required)
- Non-destructive method
- Fast analysis (high throughput of samples)
- Easy and affordable to be repaired and maintained locally

In respect of the present confirmatory technologies, at least two techniques have to be combined (e.g. HPLC and dissolution apparatus) to confirm conclusively the substandard nature of a medicinal sample.

At the time of my evaluation it became apparent that there are far more laboratory instruments available for detection of SSMs than field devices (Figure 11). Hence this reveals the lack of appropriate, easy to use and affordable technologies for rapid identification of SSMs in resource limited countries. In addition this fact further impedes the fight in the trade of these medicines (234). A wider use of appropriate field instruments may considerably support medicines quality assurance preeminently through a pre-selection process which would help to reduce the number of pharmaceuticals that require further confirmatory testing and could result in a significant reduction of analysis costs. An increased use of screening devices would provide the possibility to perform high throughput testing of medicine samples worldwide which in turn could lead to more accurate prevalence data in the global supply chain (171) on SSMs in various therapeutic areas (218). Thus neither device is entirely fit for purpose.

Presently there are mainly two established field screening tools that can be used for detection of SSMs: the CD3 and the TLC-Minilab®. The CD3 allows the comprehensive analysis of the packaging material whereas the TLC-Minilab concedes identity and disintegration but only provides semi- quantitative content assessments (185). However both instruments lack the ability of precise determination of the pharmaceutical content and the dissolution profile which is considered essential for proper analytical identification of SSMs (173).

In contrast to CD3 and the TLC-Minilab®, the portable PharmaChk device, which is currently under development, allows accurate determination of the pharmaceutical content and the dissolution profile. As both criteria for medicines quality assurance are substantial for reliably detecting SSMs (28,173), the PharmaChk device is best suited as it provides precise estimates for both analysis tests. In addition this instrument represents a simple and affordable screening method allowing a rapid monitoring of drug quality in circumstances where gold standard methods (more advanced laboratory techniques) may not be available (235). Overall, the PharmaChk is a compact screening device and can fill the apparent gap regarding analytical screening devices for detection of SSMs.

9.4 Substudy: PharmaChk assay development for Coartem®

After thorough investigation of commonly used analytical technologies for detection of SSMs, we fully recognized the essential need for research on the domain of portable screening tools. We were interested to gain more insight into the PharmaChk technique as this is the only available portable screening device that adheres to three of the four essential pillars for quality assurance of medicines (Verification of API identity, determination of API content and assessment of disintegration of the pharmaceutical formulation) and we wanted to explore its application in practice (Chapter 10.1).

In January 2015 cooperation between Novartis Pharma AG and the Biomechanical Engineering research laboratory of BU on the PharmaChk device was initiated (236). Antimalarials are the most researched group of defective medicines; it has been concluded that over 100,000 preventable deaths annually may be attributed to the consumption of substandard therapies (227).

Coartem® (a fixed combination medicine of artemether and lumefantrine) (30) was selected as the first target which represents the primary treatment for uncomplicated malaria in many countries with significant endemicity of this disease (237).

Early research on tetracycline (28) and artesunate (238) had shown the potential utility of the PharmaChk device, but it had not been validated on coartemether medicines. In the last three years the research laboratory of BU has developed an assay to specifically and sensitively identify the dose of artemether and lumefantrine in a given drug tablet (239). They isolated DNA aptamers with high affinity to the above mentioned drug substances and modified them with fluorophores to create 'aptasensors' which were integrated into the PharmaChk system for user-friendly determination of drug quality. In order to ensure that the selected aptamers were specific to the above mentioned drug substances (as opposed to excipients or degradation products), pure, high quality drug substance references were essential to the validation process. Whole tablets of genuine Coartem® were utilized as reference standards to evaluate how tablet API and excipients interact during the drug detection process. The PharmaChk assay showed accurate quantification of both APIs using absorbance. Blind tests of both APIs demonstrated accurate content quantification compared to reference samples. In addition to the evaluation of API content, the BU team further worked on revealing the dissolution profile of the APIs. In addition, the PharmaChk was tested

and further validated as screening tool for Coartem® by evaluating the quality of antimalarial samples from Zimbabwe. The research study is presented and discussed in detail in part 3 below.

The development of Coartem® assay on the PharmaChk device has added to the existing reference library of APIs on the instrument including tetracycline and artesunate (28,238). For the first time a combination drug was tested on the PharmaChk technology. Scientific research by BU made it possible to simultaneously assess the content of both APIs (artemether and lumefantrine).

10 Part 3: Quality assessment of anti-malarial fixed-dose combination tablets in Zimbabwe: Use of different screening and confirmatory analytical technologies

10.1 Introduction

In Part 1 and 2 of this research methods to identify SSMs were described. The most important adjunct to the aforementioned research outlined in part 1 and 2 was the essential activity of conducting field-based sampling and testing. The aim was to attain rapid and accurate assessment of medicine samples purchased from various suppliers and different sources in a field-based sampling approach to further assess the viability of signals generated from the screening of VigiBase®. The focus was on antimalarial medicines in Africa, where it is strongly suspected that SSMs are in circulation and are available from multiple unknown sources. This offers a significant threat to public health, and thus demanded further investigation. We chose the essential medicine Coartem® (30) as it represents the primary treatment for uncomplicated malaria in many African countries (237). Data mining analysis using Vigibase® data for the time period 1998-2017 on Coartem® revealed no excess reporting rates (EB05>2) relative to other products in the database. Although the compound has been commercially available since 1998, there have been only 555 reports of AEs from 1998-2017.

We decided to perform a research study in Zimbabwe as there have been reports of substandard and falsified medicines (240). Moreover, since 2007-2017, no quality studies of medicines were conducted in Zimbabwe. This research project is the first quality study in Zimbabwe that has been performed on Coartem® and its generic versions (241).

The overall goal of this cooperation between academic and private laboratory institution and the pharmaceutical industry was to validate a portable screening tool that could help MOH and HCPs to control and ensure access of good quality medicines to patients. In this part of the thesis the suitability of this device was assessed on purchased samples containing coartemether from Zimbabwe to test its capability and functions compared to gold- standard technology, HPLC.

10.2 Background

In March 2015, the department of Patient Safety at Novartis Pharma AG established a cooperation with the African Institute of Biomedical Science & Technology (AiBST) in Zimbabwe. This institution is specialized in forensic toxicology and is the only approved institution in Zimbabwe

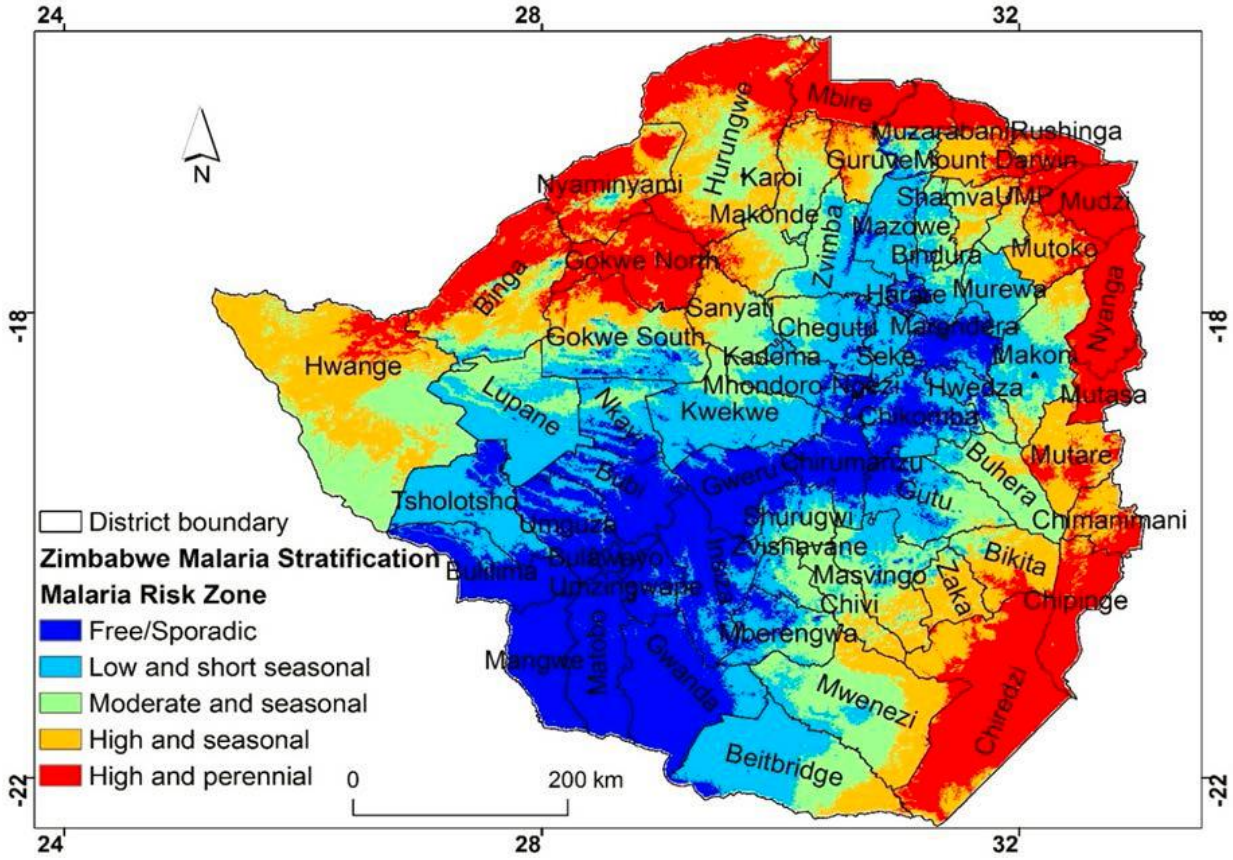
for DNA testing (242). As the problem of substandard and counterfeit medicines is a persisting threat in this country, Professor Collen Masimirembwa is “determined to tackle this growing challenge” (206) and to develop his institution to the laboratory of excellence in this field. This institution had no previous experience in detection of substandard and falsified medicines.

10.2.1 **Malaria in Zimbabwe**

In 2016, there were 216 million estimated malaria cases (95% confidence interval [CI]: 196–263 million) worldwide (243) and 445,000 malaria deaths according to World Malaria Report 2017 (244). Malaria transmission affected 91 of 196 countries worldwide in 2015 (245). Sub-Saharan Africa was the most affected region with 90% of malaria cases and 92% of deaths predominantly in children under five years (245). The malaria parasites causing the biggest malaria threat are P. falciparum (most prevalent in Africa, leading to most malaria deaths) and P.vivax which are the most common species outside of Sub-Saharan region.

Malaria in the sub-Saharan country Zimbabwe represents a major health burden with 50% of the population being at risk (8,000,000 people) specifically in the northern and eastern areas bordering Mozambique and Zambia (34) [Figure 12]. Out of the 62 country districts´, 33 are categorized as high burden malaria areas. *Plasmodium falciparum* is the main cause of this infectious disease in this region (34). According to the WHO, there are more than 400,000 malaria cases (246) each year which makes malaria the third leading cause of illness and mortality in this country after AIDS and Tuberculosis (247). In 2013, 535,931 confirmed cases and 406 confirmed deaths were reported (247,248). Considering the 2012 Malaria Indicator Survey, the prevalence of this disease was 0.4% in Zimbabwe (249). Additionally according to the map of malaria cases reported in 2015, Zimbabwe showed “insufficiently consistent data to assess trends” (250).

Figure 12 Annual Malaria Incidence Rates by District in Zimbabwe in 2016 (251)



The epidemiology of this seasonal disease differs throughout the country and varies by altitude [Figure 12]. There is year round transmission in the lowland areas (<700m) whereas the incidence in the highland areas (>1200m) is very low. The transmission time for malaria occurs mainly during the rainy season from November until April, with a peak occurring from February to April (252).

Preventive measures to tackle malaria in Zimbabwe are covering high burden disease areas with insecticide-treated nets as well as indoor residual spraying and control of malaria in pregnancy with sulfadoxine-pyrimethamine (249). Guidelines for management of malaria in Zimbabwe of December 2009 recommend the use of the combination therapy artemether-lumefantrine (coartemether) as first line treatment of simple uncomplicated malaria (247,253).

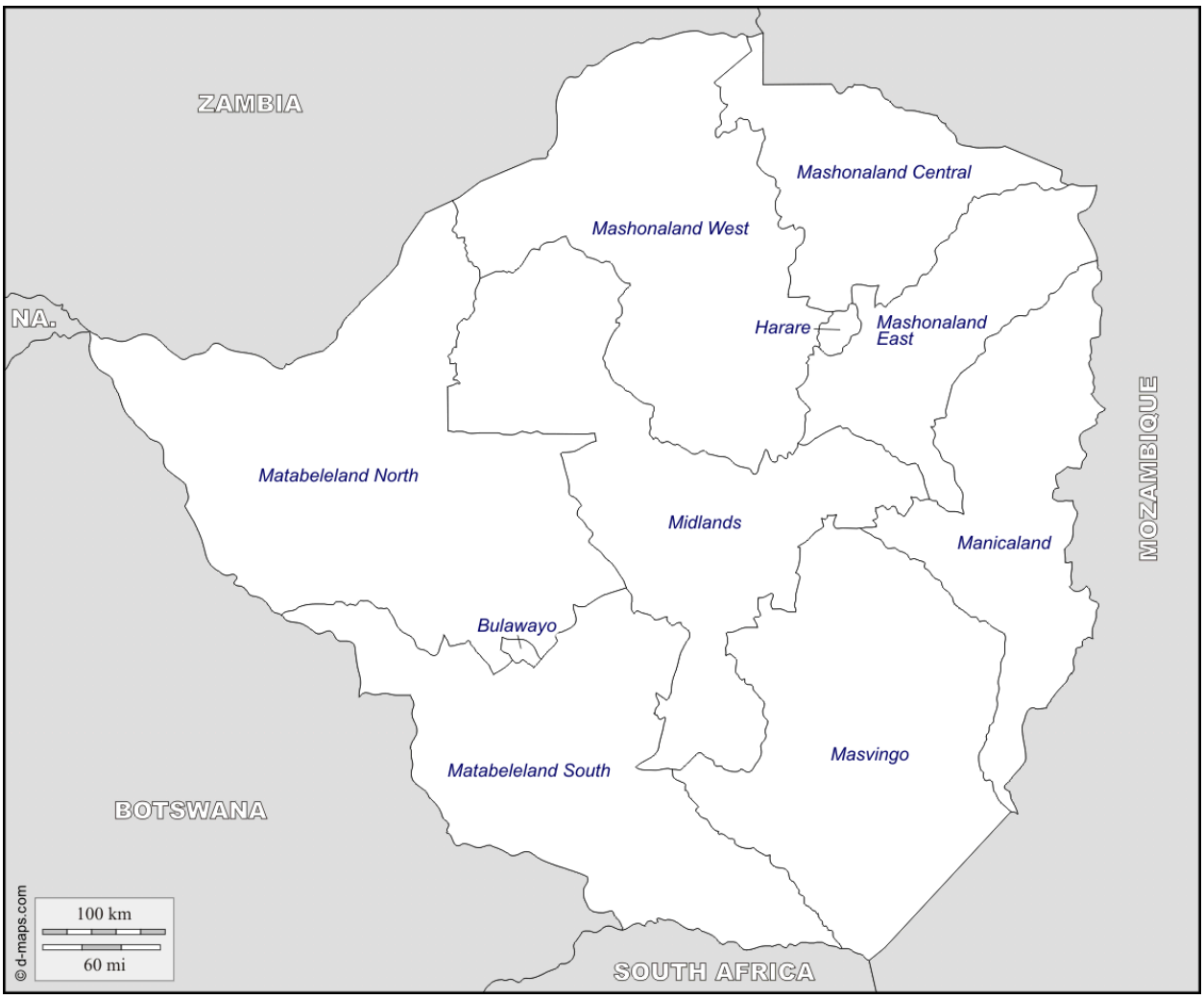
In 2009, Zimbabwe was selected as one of the Malaria Elimination 8 (E8) countries in the Southern Africa pursuing the ambitious goal “to reduce malaria incidence from 22/1000 persons in 2012 to 10/1000 persons by 2017 and malaria deaths to near zero by 2017” (249,254). According to WHO

Malaria report 2015, Zimbabwe belongs to the countries with low transmission in Southern Africa (248). In addition the WHO confirmed that in 2014 “South Africa and Zimbabwe delivered sufficient antimalarial medicines to treat more than 80% of malaria cases attending public health facilities”. Since 2011 the burden of malaria in Zimbabwe has declined due to early and improved malaria diagnosis as well as effective antimalarial treatment. From 2000-2015 the admission and mortality rates decreased by more than 75% (255) (248). Although decreasing incidence rates have been seen since 2000s, the malaria burden persists in the Northern and Eastern regions of the country, predominantly at the borders to the neighboring countries Mozambique and Zambia.

Malarious regions in Zimbabwe

The Republic of Zimbabwe consists of 10 provinces and 63 rural districts. About 70% of the population lives in rural areas (256). More than 50% of the rural districts are considered to be malarious; 30 of these districts are high risk areas and 16 are considered to be pre-elimination areas (249).

Figure 13 Provinces and neighbouring borders of Zimbabwe (257)



Zimbabwe District Health Information System 2 (DHIS2) data from 2015 revealed that about 83% of the malaria cases and 61% of the deaths caused by malaria occurred in sustained high burden areas situated along the Zimbabwe-Mozambique border: Manicaland with 33%, Mashonaland Central with 15% and Mashonaland East with 14% of the malaria deaths (252). Manicaland province was the area with the highest number of all malaria cases in this country (42%) (249,258).

10.2.2 **Health care system in Zimbabwe**

The health care system in Zimbabwe is divided into public, private (259,260) and traditional sectors. The public sector which again is divided in national, provincial, district and primary/rural levels, represents the “major provider of health services” and consists of Ministry of Health and child care, local government and mission hospitals. The Zimbabwean government owns about 70% of the healthcare facilities, whereas the private sector owns about 30%. Most of the population uses state and mission hospitals and clinics which are less expensive (261). In 2008, 65% of health care services were provided by the public sector in Zimbabwe (262).

According to data compiled by the Community Working Group on Health (CWGH), the government spent 6% of its 4.1 billion $US national budget on public health in 2015. This budget allocation remains below the agreed target set by the African union (Abuja Declaration’s goal of 2001) of 15% of the country’s total budget to the health sector (263). The majority of the population in Zimbabwe cannot afford basic health care services (264).

The Zimbabwean government tends to favor budget allocations to the two wealthiest cities, Harare and Bulawayo. This is reflected by the number of health care facilities in these two cities (265). The capital Harare (population 2,123,132) comprises 50% of the health care facilities of Zimbabwe including 246 registered pharmacies, 9 hospital pharmacies and 54 industrial clinics. In total there are 538 pharmacies, 16 hospital pharmacies and 190 industrial clinics in Zimbabwe. Due to the relatively unstable economic situation in the country and an unemployment rate of 70% in 2013, the number of informal drug retail outlets (266) is increasing (267).

Less than 1% of the population in Zimbabwe (16,813,229 inhabitants) (268) can afford health insurance. The government health insurance covers health care for military, military veterans, teachers, government employees, health care workers, and individuals living in extreme poverty. In addition employer based and private health insurances as well as company-provided health insurance (for employees of mining companies and large agriculture companies) do exist (265).

10.2.3 **Affordability of medicines and access to patients**

In the last 20 years the Zimbabwean health care system has faced many political, social and economic challenges but it has recovered during the last five years (269,270). However, the current economic situation of the country (due to hyperinflation and "dollarization" (265)) is not strong enough to support all public health needs. Many health workers went abroad for better positions and salaries, which has led to severe human resource shortages in the public health care system (265). The weak economic situation in Zimbabwe has led to stock-outs of essential medicines, medical supplies, infrastructure, and a reliance on donor-supported programs particularly for infectious diseases including malaria and AIDS. The majority of the health initiatives are funded by various international donors such as Global fund, UNICEF (271). The Zimbabwe National Drug Policy has still not achieved its goal of 90% availability of essential medicines (e.g. amoxicillin, ciprofloxacin) in the country (272). Medication prices are relatively high in Zimbabwe and impede the accessibility of medicines to patients with low incomes (272). The latest survey on medicine prices in Zimbabwe in 2005 applied by the WHO/HAI (Health Action International) concluded that there were considerable price increases from manufacturer to wholesaler and finally to the patient. There was a markup of 40% from the wholesaler adding up to 50% for import, insurance and freight fees (273).

There is also a considerable price discrepancy between the public and private sector (273), with the costs of some generic medicines 22.3% higher than those in state hospitals (272). As an example "the lowest paid government worker would need 4.5 days' wages to purchase asthma treatment in the private sector versus 3 days to get generic medicines for asthma in the public sector" (273). Gavaza et al. revealed (272) that dispensing doctors from the private health care facilities in Zimbabwe charged the highest prices whereas the public hospitals charged the lowest prices for the medicines investigated in the study. In addition the price of innovator brands was three times as expensive as the cost of generic versions purchased in the private sector (272).

The dilemma is, that not all medicines can be accessed in the public sector, so patients have to go to private health care facilities to obtain the required medication (272).

10.2.4 **Manufacturing of medicines in Zimbabwe**

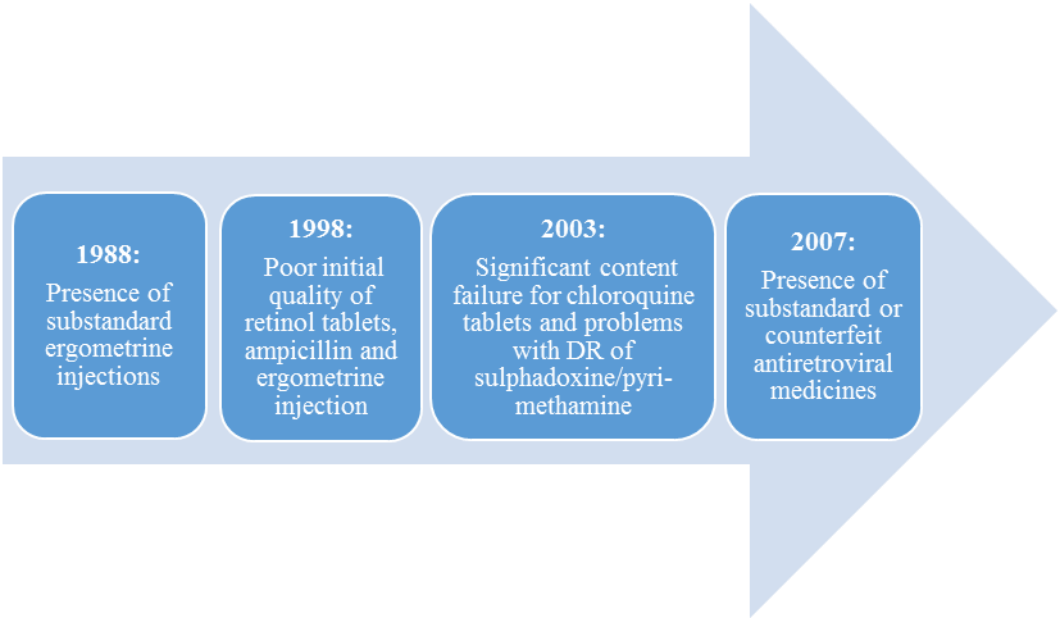
According to MCAZ (registered health care facilities in 2015) there are 13 licensed pharmaceutical manufacturers approved by Zimbabwe government that are GMP certified out of which only one meets the WHO prequalification requirements (274). The domestic manufacturers cover about 50% of the essential medicines (259). The acceptance of generic medicines is very high on the pharmaceutical market in Zimbabwe. This is reflected by the number of prescriptions as well as the amount of medicines imported to the country, mainly from India. According to the price survey from 2005, generic imported drugs are cheaper than the local manufactured medicines. The results of this survey showed that from 43 investigated medicines, no innovator branded medicinal product was available in the supply chain of this country, meaning that all medications had to be imported.

First line treatment for uncomplicated malaria is the fixed-combination drug artemether-lumefantrine (coartemether). Currently there is no local manufacturer for this medicinal product in Zimbabwe (273). All registered versions of coartemether medicines (excluding Coartem® which is the innovator brand) are generic medicines imported from India.

10.2.5 **Substandard and falsified medicines in Zimbabwe**

A comprehensive review of the literature has revealed a high risk of availability of substandard and counterfeit medicines in pharmacies, hospitals and drug outlets in Zimbabwe (37,249). The prevalence of substandard/falsified medicines in this country is estimated to be between 11-44% (median 28.5%) (275). This figure represents a very broad range probably due to the presence of only a limited number of studies on the quality of medicines and potency assessments in the last 30 years. However none of these studies used random sampling and therefore the actual prevalence of falsified and SSMs is unknown (6). All of these studies illustrated below (Figure 14) show the circulation of poor quality medicines in this country.

Figure 14 Summary of studies on medicines quality and potency assessments in Zimbabwe



While there are few prevalence surveys on SSMs in Zimbabwe since 1988 (Figure 14), these only analyzed limited product characteristics such as content API% and dissolution rate (DR) (276).

The first field study to investigate the presence of SSMs in Zimbabwe was performed in 1988. The parenteral ergometrine medication was intended to prevent maternal death due to post-partum haemorrhage. It turned out that the potency of parenteral ergometrine was severely affected by storage at ambient temperatures in tropical countries instead of being stored under refrigeration [between 2°C and 8°C] (36) (277). In 1998, another trial on 13 essential medicines concluded that medicinal products instability (due to storage of transport) was rare and that poor initial quality poses a much more serious problem (278). In 2003, a pilot study on quality of antimalarials was performed in Zimbabwe and seven other African countries. The study revealed significant content failure for chloroquine tablets as well as problems with the dissolution rate of sulphadoxine/pyrimethamine (279). The survey on quality of antiretroviral medicines in 2007 also revealed the presence of substandard or falsified antiretroviral medicines in Zimbabwe (280).

In Zimbabwe, the first antimalarial drug resistance cases were reported in 1984 (35). The infiltration of poor quality medicines containing subtherapeutic concentrations of the Zimbabwean

market may contribute to the development of antimicrobial resistance (6). There is not enough field evidence available but SSMs with reduced API content or bioavailability, resulting in low drug levels are suspected to be a relevant driver for development of drug resistance and failure of efficacy and may "thereby lead to the wider spread of" malaria (4). Drug levels in the blood are the key variable for determining patient outcome and resistance to most infectious diseases (281).

10.3 Aims and objectives

At the present time there is paucity of research on the quality of locally available antimalarial medicines (282) in Zimbabwe "…where the market for antimalarials is substantial…" (282). This research project aimed to cover a selected cross-section of the country's registered and potentially illicit medication distribution channels and to assess the quality of the essential antimalarial drug Coartem® and its generic versions in the private health sector in Zimbabwe. The secondary objective was to evaluate the accuracy of the PharmaChk device in a real-world setting regarding quantification of artemether and lumefantrine content compared to state of the art technologies. The tertiary objective was to build laboratory capacity in Harare in collaboration with AiBST to identify substandard and falsified antimalarials.

The "association between health care costs and quality is one of the more controversial topics in health policy" (283). The exploratory objective of this survey was to investigate the price of Coartem® and its generic versions in order to determine if there is an association between the cost of medicines and medicines quality. In public health care facilities the fixed-dose combination medicine of Coartem® is provided for free to the patients. In addition, this study intended to build up laboratory capacity to support the Medicines Control Authority of Zimbabwe (MCAZ) to detect poor quality medicines. According to the current President and Chief Medical Officer, Professor Collen Masimirembwa of AiBST, there has been no similar study conducted on coartemether medicines in Zimbabwe, so far.

10.4 Ethical approval and permissions

The legal framework for this research study was agreed upon by all participating parties. The approval to conduct this study in Zimbabwe was requested from AiBST director Prof. Masimirembwa and obtained from MCAZ in September 2016.

10.5 Material and methods

The study was carried out in malaria-endemic areas of Zimbabwe to study the quality of coartemether medicines using different screening and confirmatory technologies in order to classify the purchased samples in good quality, substandard and falsified. This research study targeted the six approved coartemether medicines in Zimbabwe for uncomplicated malaria including Coartem®, Artefan, Combiart, Lumartem and Lumither in 20/120 mg tablets and Komefan in both 20/120mg and 40/240mg (MCAZ registered medicines 2016). The medicine samples were purchased from retail and hospital pharmacies and the informal market of the private sector.

10.5.1 Study activities overview

Coartem® and its generic versions were purchased by mystery shoppers between 6-14. Feb 2017 from 16 cities throughout Zimbabwe and between 28. March - 3. April 2017 from Harare and Chitungwiza and delivered to the analysis laboratory in Harare. Purchase locations included retail pharmacies and hospitals from the private sector and unlicensed drug outlets. The selected timeframe of the sample collection coincided with the peak malaria transmission season (249). During the sample collection timeframe from February until April 2017, heavy rain falls in Zimbabwe lead to an increase of malaria incidences “134,224 cases and 194 deaths…if compared to 2016 at this same time only 80,964 cases were reported” (284,285).

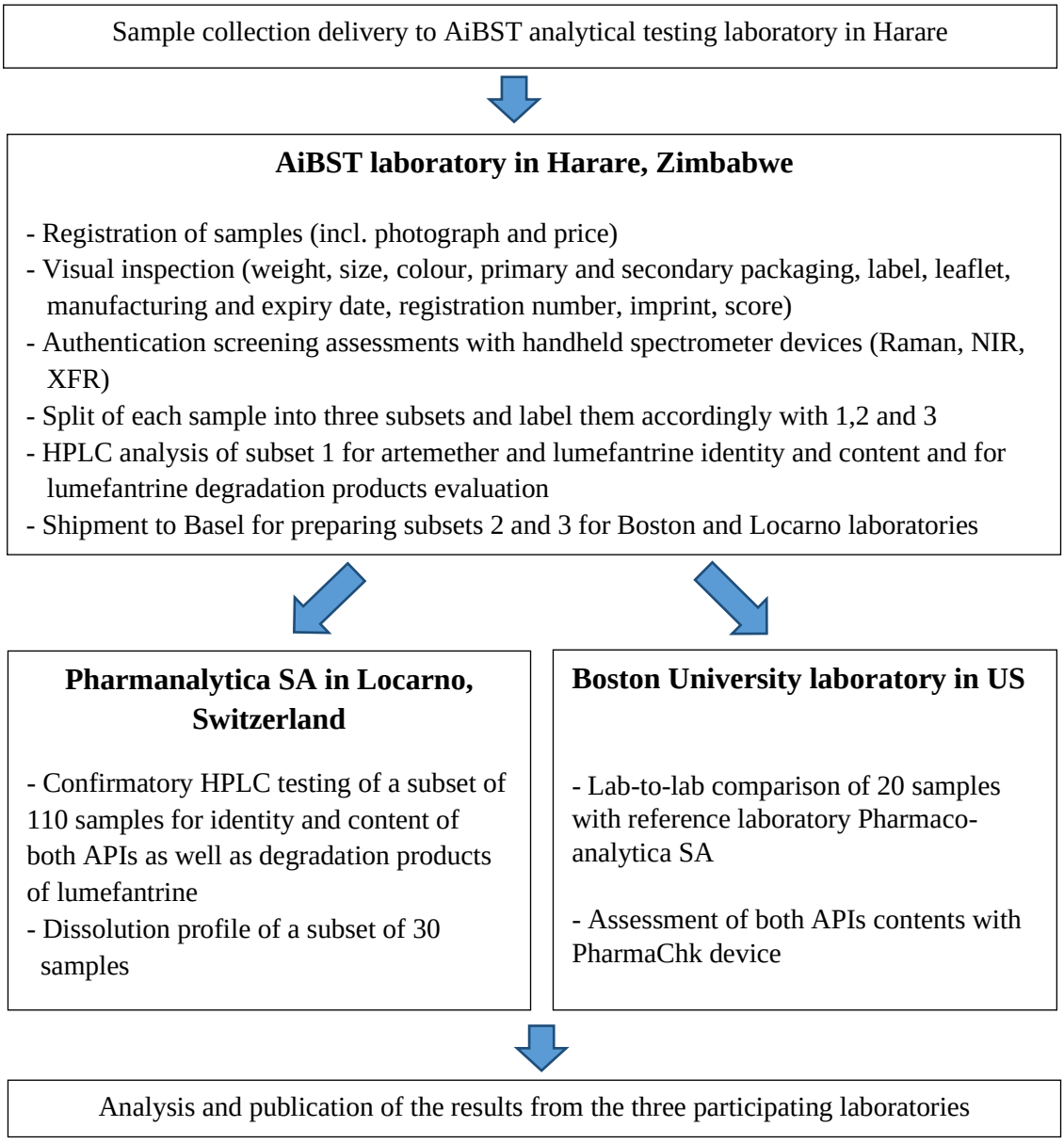
All samples were logged and labeled with a unique number linking it to a database containing detailed description of the medicinal samples (6). All acquired samples were “stored under nominal conditions” (in their respective primary and secondary packaging at room temperature) (177). Each collected medicine sample consisted usually of 24 tablets which were then divided into three subsets (8 tablets for analysis per laboratory institution) in order to test it in the three

participating laboratory institutions to assess how many samples were of good quality, substandard or falsified. Identification of potential falsified medicinal samples were based on packaging inspection (6) and rapid authentication assessments with Raman, NIR and XFR handheld devices. Identification of potential substandard samples were based on physical testing (e.g. considerable weight and size deviations of tablets within a blister) and chemical analysis results (e.g very low or high levels of API, the presence of impurities and/or degradation products outside of acceptable limits or issues in the dissolution profile).

After completing tracking, visual and authentication assessments at AiBST laboratory in Harare, subset 2 and 3 of the collected samples were shipped to the Novartis Locarno laboratory in Switzerland (reference laboratory) for confirmatory HPLC testing, and to the BU laboratory in the US for verification of the results on the PharmaChk device. Two different sample definitions were used for this study. At BU and Locarno laboratories samples of packages with same batch ID sourced from the same pharmacy were defined as one individual sample. For the authentication assessments, in particular to identify falsified coartemether, the forensic definition of a sample was used, by which every package was considered as an individual sample disregarding batch ID and pharmacy location.

For QC purposes, a blinded interlab assay comparison (6) was performed on 20 medicine samples at AiBST laboratory in Harare, Zimbabwe, and the BU laboratory to assess the equivalence performance of performed assays to the HPLC results from the reference institution in Locarno, Switzerland. Moreover confirmatory testing was conducted in the reference laboratory in Locarno to evaluate the reliability of the results from AiBST and the BU laboratory. After completion of the analysis process, the results were compiled and the outcomes of the three research questions will be published and reported to MCAZ. The following graph (Figure 15) summarizes the activities of the research project in Zimbabwe.

Figure 15 Study activities overview

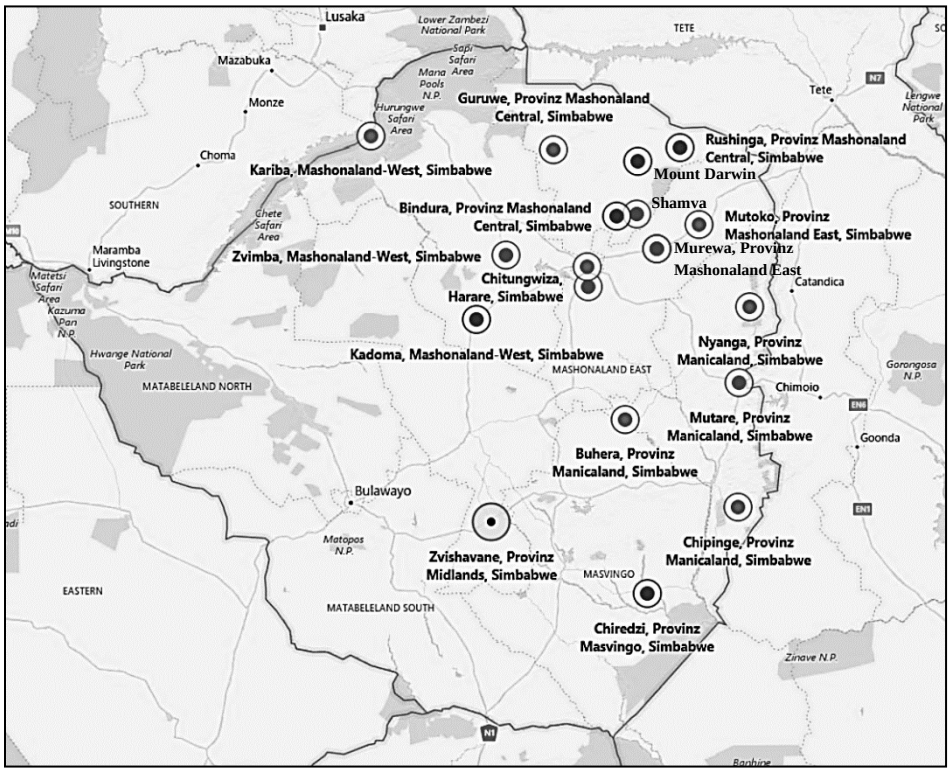


10.5.2 **Sample collection**

Selection of sites

This study was performed in seven out of a total of ten provinces in Zimbabwe. We targeted 80 drug collection sites in 17 cities (Figure 16) across the 7 study provinces in Zimbabwe for the procurement of Coartem® and its generic samples (based on the list of registered health authorities from MCAZ in 2015). This included public and private health care institutions and the informal market (outlets not registered with the MOH) (282). All private and registered retail and pharmacies in clinics present on the Zimbabwean health authority list of healthcare institutions (MCAZ list 2015) were eligible for inclusion in this pilot study (6).

Figure 16 Selected study locations (286)



We focused on high and moderate risk zones with malaria incidence rates of 101-405 and 6-100 (287) and selected the following cities as there were historical entomological data available for these regions (morbidity and mortality data by district in 2015) (287): Buhera, Chipinge, Mutare, Nyanga, Bindura, Guruve, Mount Darwin, Rushinga, Shamva, Murewa, Mutoko, Zvishavane,

Chiredzi, Kariba, Zvimba, Harare and Kadoma (Figure 16). We randomly selected eight licensed hospital- and 48 community pharmacies in each of the above mentioned cities in the provinces Mashonaland Central, East and West, Manicaland, Midlands and Masvingo. Moreover we also looked for informal markets in the selected cities. Most of the sample collection sites were in the malaria high risk zones Mashonaland and Manicaland with the highest malaria mortality rate of over 60% (287). We also included Harare which is considered as a low malaria risk area (malaria incidence 0-5) (288), but as mentioned above almost half of the health facilities of the country are present there.

Convenient and random sampling

Convenient sampling is a technique that selects sites based on convenient accessibility and proximity (247). If sufficient sample size is ensured, random sampling provides reliable estimates of the prevalence of outlets selling poor quality medicines and their distribution in the defined area (289). However according to literature, only very few studies (289) have applied random sampling, as this sampling method is expensive, time-consuming and requires complete lists of target outlets locations (290).

In this research project we applied the two most common sampling approaches: convenience and random sampling method (270). For the sample collection in February 2017, the sites from the private health care sector were targeted from the MCAZ list using the application Microsoft Excel as the random number generator. With regard to the convenience sampling approach, we considered the MCAZ list from February 2017 of the registered medicine outlets in Harare and Chitungwiza. For Harare, we grouped the locations in four zones, North, East, South and West and tried to visit as many locations as possible in one week. Sample collection in Chitungwiza was performed in one day and we considered all sites of the MCAZ list.

Covert mystery-shopper approach

Mystery shoppers are individuals who visit retail stores, acting as customers to collect information about the stores' display, prices and quality of the products (291,292). In a covert approach the identity and purpose of the buyer is not known by the outlet being evaluated; the sellers are blinded

(290,293). This approach avoids potential bias (compared to the overt approach) due to shopkeepers holding back the drugs that are more likely to be falsified or substandard.

In this survey, the purchase of the medicine samples was performed covertly in all specified locations with trained mystery shoppers who were mostly nationals of the country (290). At each site, the mystery shopper ascertained if the medicine was available, then recorded the price, name of the outlet and other information requested by the survey objectives (272,290). We chose this market research tool to reduce the risk of obtaining biased samples in our study (293,294). If sellers are concerned that their stock contain poor quality medicines and that the buyer is potentially linked to the NMRA, this may influence their selling behavior and the risk of concealing falsified and SSMs is increased (290).

Sample size estimation

As described above the prevalence of substandard/falsified medicines in Zimbabwe is estimated to be between 11-44% (median 28.5%) (128). We estimated the sample size for this study assuming the median prevalence of 28.5% (p=0.285). To determine the actual prevalence of outlets selling substandard and falsified medicines in Zimbabwe with a precision of 5% (e=0.05) with 95% confidence intervals (z=1.96), we used the following formula (11,295):

$$n=\frac{z^2(pq)}{e^2}=\frac{(1.96)^2*(0.285)*(0.715)}{(0.05)^2}=313.13$$

As the estimated prevalence for substandard/falsified medicines in Zimbabwe represents a broad range (11-44%), we also calculated the sample size for the lower and higher estimated prevalence rate.

Assessment of the actual prevalence of outlets seeing substandard and falsified medicines assuming that the estimated prevalence of SSMs in Zimbabwe is 11%:

$$n=\frac{z^2(pq)}{e^2}=\frac{(1.96)^2*(0.11)*(0.89)}{(0.05)^2}=150.44$$

Assumption that the estimated prevalence of SSMs in Zimbabwe is 44%:

$$n=\frac{z^2(pq)}{e^2}=\frac{(1.96)^2*(0.44)*(0.56)}{(0.05)^2}=378.68$$

n= sample size

z= standard error associated with the chosen level of confidence (1.96)

p=estimated percent in the population

q=100-p

e= acceptable sample error

Thus we would need a random sample size (n) of at least 151. This meant that procurement from at least 151 different outlets selling coartemether medicines would be required to obtain an objective estimate of the prevalence of those selling substandard and/or falsified coartemether drugs at one time point in Zimbabwe (11).

Selection of medicines to be purchased

All six targeted coartemether medicinal products had achieved WHO prequalification (296). At each site, a minimum of two packages [one served as backup for possible additional analysis (282)] of each of the six products were purchased. If the respective medicine was not available at the targeted site, the mystery shoppers went to other retail pharmacies to purchase the required samples.

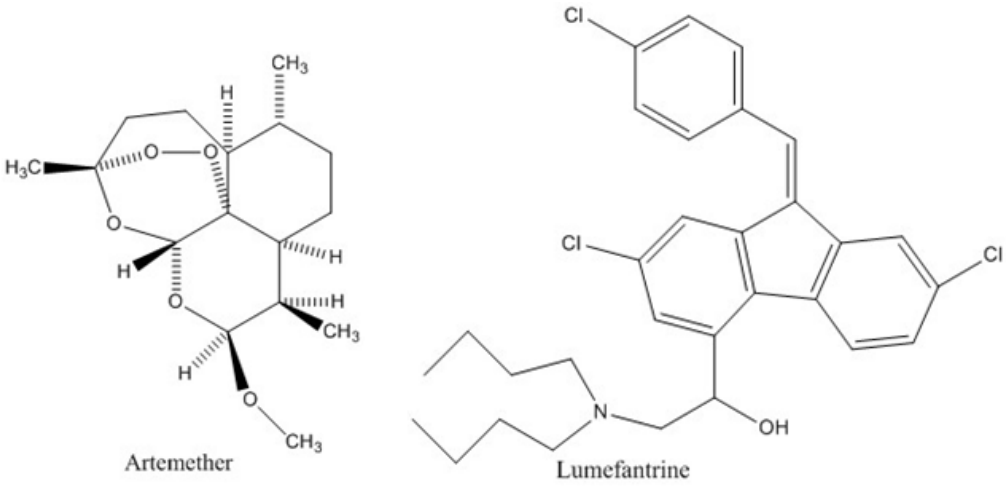
In July 2015 MCAZ issued a recategorisation of antimalarial combination drug artemether-lumefantrine from a Prescription Preparation (PP) to a Pharmacist Initiated Medicines (PIM) "in line with the "New WHO recommendations and the current National policy on Malaria" (297). Pharmacist Initiated Medicines (PIM) are defined as "medicines that may be initiated and dispensed by a pharmacist without a prescription" (298). In both private and public health care facilities this combination drug should be provided to patients after confirmation of marlaria infection with a rapid diagnostic test (RDT) (253). For this research study a physician from AiBST hospital issued the required prescriptions to allow the mystery shoppers to purchase the medicinal products. Permission was granted from MCAZ. To avoid misuse of these prescriptions (use of prescriptions other than in this project), the mystery shoppers were asked to track the collection with receipts from the pharmacies confirming that the drug was obtained.

Coartem® brand tablets (containing 20mg artemether and 120mg Lumefantrine) and the respective reference substances of both APIs were provided by Novartis Pharma AG to the BU and the Harare laboratory in order to calibrate the devices.

Details of the APIs

The antimalarial agent used in this research study included a fixed-dose combination of two APIs artemether and lumefantrine (ratio of 1:6) (Figure 17). Both components are crystalline powders but differ in colour (artemether is white, lumefantrine is yellow) and solubility (lumefantrine is a highly lipophilic compound) (299). Artememether and lumefantrine are blood schizontocides and inhibit nucleic acid and protein synthesis in erythrocytic stages of Plasmodium falciparum (299). The elimination of artemether and active metabolite Dihydroartemisinin (DHA) from plasma is much faster (half-life two hours) than the elimination of lumefantrine (elimination half-life 3-6 days) (299). Currently there is no monograph for Coartem® dispersible tablets in the British Pharmacopoeia (BPh), United States Pharmacopoeia (USP) or Japanese Pharmacopoeia (JP), only a draft international monograph is available from WHO (300).

Figure 17 Chemical structures of artemether and lumefantrine (299)



10.5.3 **Drug Quality Assessments**

We performed several tests to evaluate the quality of Coartem® and its generic medicinal products collected in a field study in Zimbabwe.

Visual evaluation and physical testing

All medicine samples underwent visual and physical inspection for labeling and packaging before physico-chemical quality testing (23) was performed. Visual assessments included weight, size measurement, color and presence of score and imprints of the procured tablets. The primary packaging of each medicinal sample was scanned electronically and/or photographed and compared against authentic packaging, wherever available (6). Weight measurements were performed by using an analytical balance (precision: 0.00 mg). We used a digital caliper (precision: 0.00 mm) for measuring tablet thickness and diameter. Coartem® tablets were used as reference with specification ranges for weight of 0.228-0.252g, tablet thickness of 3.0-3.4 mm and diameter of 9.1-9.2 mm (177).

Qualitative and quantitative screening assessments of the collected samples

Qualitative screening tests of collected samples

Handheld spectroscopic devices such as Raman, NIR (Table 5) and XFR (from ThermoFisher Scientific) use qualitative methods (177) and can quickly and accurately scan a medicine sample and determine its legitimacy (177). These techniques do not destroy the sample and allow a high throughput of samples (173,177). The application of NIR spectroscopy can identify subtle changes in the chemical composition of a medicinal sample by degree of similarity to the identified compound and detect differences between genuine and falsified drug products. Moreover, Raman spectroscopy allows uncovering slight changes in chemical structure and morphology of the tested samples (301). The XRF spectrometer allows rapid qualitative assessment of the elemental composition of materials (302) by measuring the characteristic fluorescent X-rays emitted from each of the elements present in a sample when it is excited by a primary X-ray source (303) .

As each of the collected sample packages were divided into three subsets (Figure 15), for the authentication assessments (Raman, NIR and XFR), one tablet was randomly taken from each of the three subsets and Raman, NIR and XFR analysis were performed (177,304). Before analysis of the investigated medicine samples, a reference spectrum for Coartem® was stored in the instrument library of Raman and NIR devices. When a medicinal sample containing coartemether was run, the result was displayed on the screen indicating whether the product “passed” or “failed” and therefore confirming whether the generated spectrum matches the one of the reference product Coartem®. A probability value describes how closely the spectrum of the analyzed sample is to the signature spectra of genuine Coartem®. The tested sample passed if its probability value was higher than 0.05 (Figure 18). If the sample failed (Figure 19), the sample spectrum was compared with other signatures stored in the library and the closest matches were displayed on the screen along with the spectra of Coartem® and the sample spectrum (305). The spectra were compared to the original brand reference (177).

Figure 18 Raman spectrometer analysis of a Coartem® tablet - Pass result and spectrum comparison with Coartem® reference spectrum

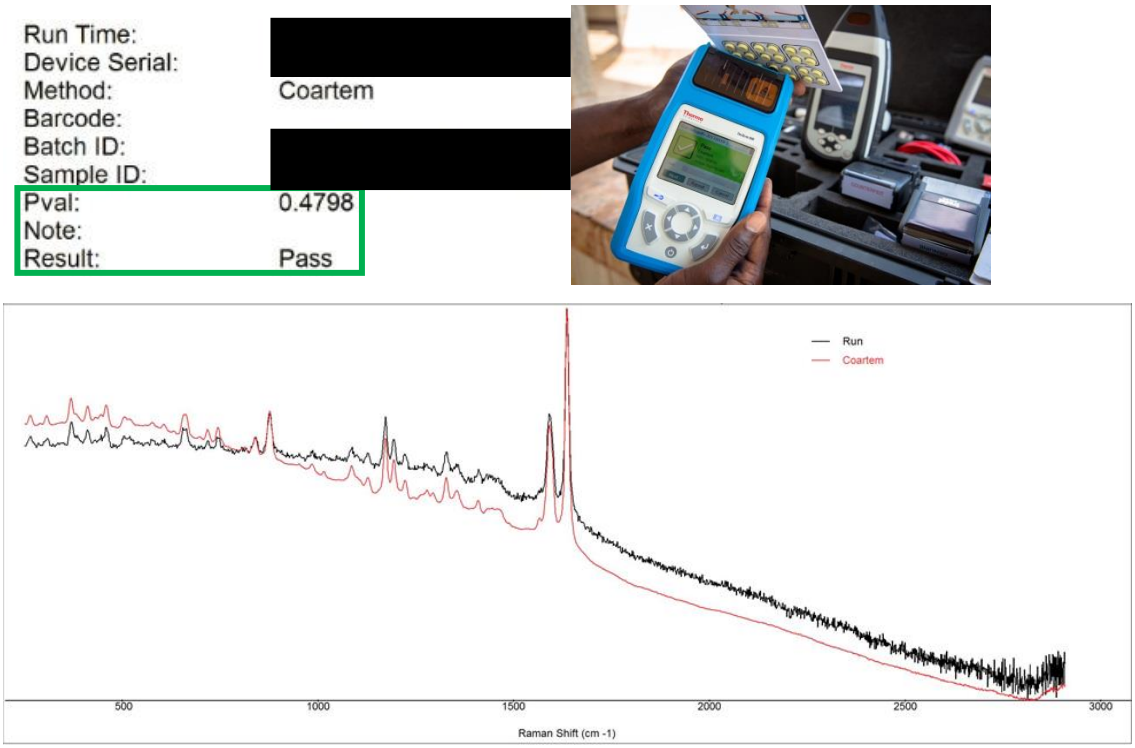
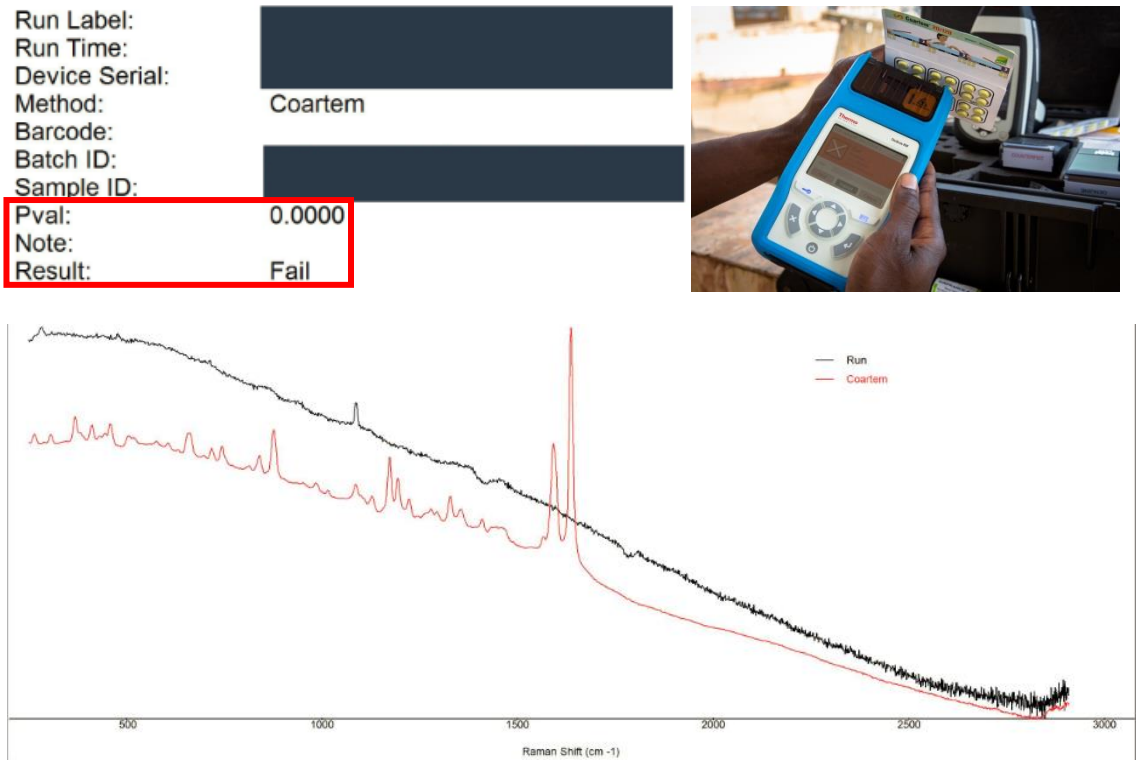


Figure 19 Raman spectrometer analysis of a Coartem® tablet - Fail result and spectrum comparison with Coartem® reference spectrum



Quantitative screening test of collected samples

Existing field technologies in medicines screening have not yet been able to accurately quantify the API content. PharmaChk is a low-cost, portable drug screening device which allows API quantification and API kinetic release. This instrument is based on a microfluidic, flow-through technology that uses fluorescent reporters to specifically quantify API molecules from a solid formulation in solution (173).

After arrival of subset 2 of the medicinal samples at the BU laboratory, one tablet from each sample was randomly taken and tested for API content using the PharmaChk device. Each sample was measured relative to an authentic reference sample (177).

Confirmatory assessments

Content and degradation testing was carried out on subset 1 of the samples in Harare with gold standard technology HPLC using the Novartis monograph. Content evaluation determined the amount of both APIs (artemether and lumefantrine) present as a percentage of the declared strength in the product data sheet. Analysis of degradation products on the collected medicine samples was performed to differentiate between medicines that were substandard due to poor manufacturing practice versus degradation post-manufacture (6).

As first steps of the HPLC analysis, sample tablets were pulverized and extracted in an appropriate solvent. Thereafter the solvent extracts were sonicated followed by centrifugation, and finally the supernatant was injected into the HPLC system for determining the content of both APIs (6). The API amounts were assessed by comparing the amount of API in eluents of each dissolution sample against a calibrated standard for artemether and lumefantrine after HPLC analysis (6).

As mentioned above, subset 2 was sent to the BU laboratory for API content analysis with PharmaChk device.

Subset 3 of the samples was sent to the Pharmanalytica SA laboratory in Locarno, Switzerland (a GMP accredited laboratory) for HPLC analysis confirming content, degradation and dissolution profiles (6). All confirmatory tests were conducted according to Novartis monograph.

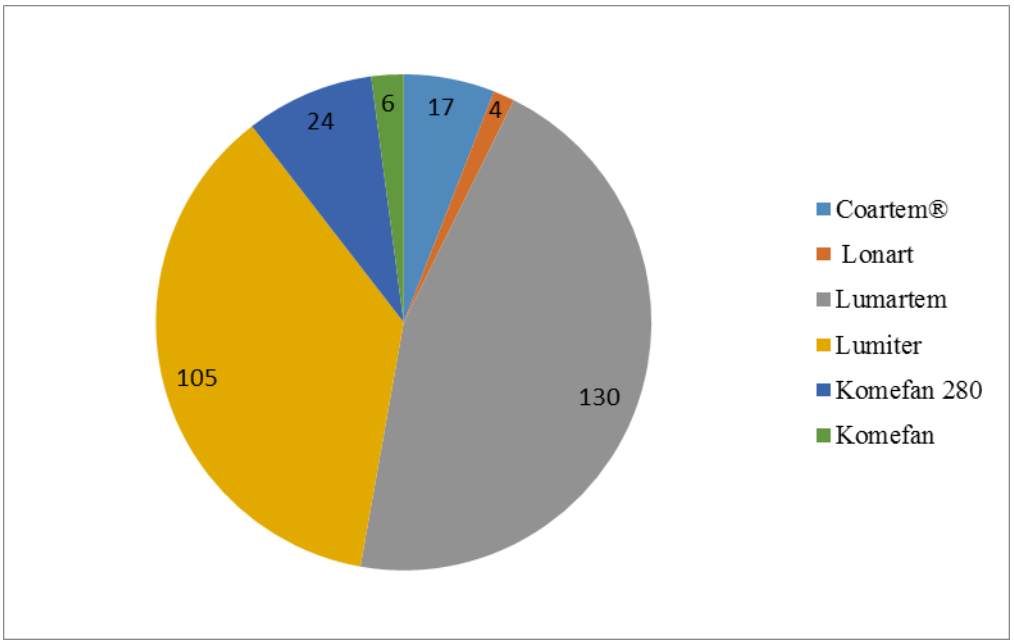
11 Results

11.1 Numbers of samples collected: Random sampling versus convenient sampling

Initially we planned one collection round of medicinal product samples using random sampling in 17 cities between February 6-14, 2017. As only 76 medicinal packages of Coartem® and its generic versions could be acquired from 86 drug outlets (including retail pharmacies, pharmacies in clinics and informal outlets), we conducted a second round of sample collection where we performed convenient sampling. This took place from March 28 to April 3, 2017, in Harare and Chitungwiza where we acquired 210 packages from 114 visited drug outlets. In total 200 health care facilities including informal outlets were visited at two different time points across 7 of 10 provinces of Zimbabwe, and a total of 286 (76 + 210) samples were collected.

It is noteworthy that the essential medicine coartemether was provided free of cost in all public hospitals and health centres with a prescription. We did not obtain any medicines from visited public hospitals (with the exception of one facility) as these did not serve retail customers or dispensed antimalarial drugs unless thepatient provided a positive rapid diagnostic test (RDT). Informal markets were found in Harare, Shamva, Kadoma, Buhera and Murehwa, however no antimalarials were sold. The pie chart below (Figure 20) illustrates the number of purchased packages of the different brands. The most common generic brand was Lumartem. Two of the targeted six registered coartemether medicines (Artefan and Combiart) (306) were not available at any healthcare facility at both collection time points. Indeed, most of the sellers did not even recognize the names of these two branded generic medicines. In addition, one of the purchased brands (Lonart) was not licensed for use in Zimbabwe. These were sourced from two retail pharmacies in Harare and Kadoma.

Figure 20 Name and number of procured medicinal packages of coartemether from 17 cities of Zimbabwe



In total, we obtained 286 packages of coartemether (N=285 packages from private sector and 1 package from the public sector) and 2 packages of sulfadoxine and pyrimethamine as requested medicine combination was not available at one of the sites. These two packages of sulfadoxine and pyrimethamine were excluded from further analysis as the scope of this project was the evaluation of quality of coartemether medicines. In most of the pharmacies only one of the five registered coartemether brands was available. The 286 medicinal packages of coartemether were considered for visual inspection and authentication assessments (Raman, NIR and XFR). For the confirmatory analysis as well as for the screening test with PharmaChk device a subset of the collected samples was analyzed. The original brand Coartem® was considered as reference for the analysis and provided by Novartis Pharma AG to all participating laboratories.

11.2 Visual inspection

11.2.1 Physical characteristics: Weights and dimensions

Table 6 presents the weights and dimensions of the 17 collected Coartem® brand tablets relative to the range expected for the genuine tablets (177). Any tablets measurements falling outside the

acceptable range would be considered as “failed”. Weight and dimension measurements reveal that all collected Coartem® samples were within the acceptable limits.

Table 6 Weights and dimensions of purchased medicine samples of innovator brand Coartem®

Case number	Diameter (mm)	Tablet thickness (mm)	Weight (g)
Expected dimensions	9.1-9.2 mm	3.0-3.4 mm	0.228-0.252g
HA-007-01	9.16	3.2	0.245
HA-008-01	9.13	3.16	0.243
HA-023-1	9.08	3.22	0.242
HA-088-1	9.08	3.18	0.244
HA-089-1	9.11	3.18	0.241
HA-090-1	9.11	3.17	0.242
HA-091-1	9.1	3.16	0.242
HA-096-1	9.11	3.17	0.242
HA-097-1	9.1	3.19	0.243
HA-153-1	9.15	3.18	0.241
HA-185-1	9.17	3.2	0.243
HA 213-1	9.16	3.16	0.240
HA-214-1	9.14	3.22	0.245
BI-005-1	NA	NA	NA
BI -006-1	9.13	3.13	0.242
ZA003-1	9.1	3.21	0.244
CI001-1	9.12	3.14	0.239

NA: Not available

Table 7 Average weights and dimensions of purchased medicine samples of generic versions of Coartem®

Product name	Diameter (mm)	Tablet thickness (mm)	Weight (g)
Lumartem	10.10	3.57	0.351
Lonart	10.28	4.46	0.332
Lumiter	8.93	3.59	0.250
Komefan	9.10	3.90	0.305
Komefan 280	11.64	4.88	0.601

There were no reference tablets for the registered and prequalified brands (Komefan; Komefan 280; Lumartem; Lumiter) available, therefore the WHO prequalification documents (Part 2b-Visual appearance of the product and part 4-Summary of Product Characteristics) were used as guidance. According to these guidelines (307–311) all medicine samples from registered and prequalified brands (Komefan, Komefan 280, Lumartem, Lumiter, Coartem®) passed the visual inspection including colour and diameter. All sourced tablets were yellow coloured, circular, flat, beveled-edged and uncoated. All scores of collected samples passed except of Lumiter who showed a different score than the WHO prequalification documents [with one side plein and other side "MPL"; collected samples are plain on both sides] (312). But as there were no reference tablets available for Lumiter, a definitive assessment could not be made. The weight and thickness of the other registered brands could not be evaluated as there was no information available in the WHO prequalified documents. Table 7 revealed that there was a match with the weight and dimensions of the collected Coartem® samples in only two cases (average of Komefan diameter result and Lumiter average weight result).

11.2.2 **Packaging inspection**

The inspection and comparison of the packaging of collected Coartem® samples against available Coartem® genuine tablets revealed that there were no obviously falsified packages. For all other registered brands drug packaging appeared appropriate with correctly stated dose, type of drug, batch number, expiration date and manufacture date (282) as well as the MCAZ registration number. However the original drug packaging from the manufacturer was not available for comparison (6).

For 244 medicine packages (85%) primary packaging was available. It was also found that for only 192 packages of 286 packages (67%) the package insert was available. All procured medicine samples, except the original brand, were manufactured in India.

Expiry information

Four medicine packages (1.4%) were found to be expired at the time of purchase. No expiration date information was available for 4 medicine samples (1.4%) which were dispensed as 24 loose tablets in a plastic bag without packaging information.

11.3 Authentication screening tests

11.3.1 Raman spectrometry results

In total, 92% (N=262) of the samples passed the Raman authentication test; in 6% (N=17) of the cases the results were inconclusive. In 1% (N=4) of the cases, the samples failed the Raman test.

11.3.2 NIR spectrometry results

In total, 62% (N=177) of the samples passed the NIR authentication test; in 25% (N=71) of the cases the results were inconclusive. In 12% (N=35) of the cases, the samples failed the NIR analysis.

11.3.3 XRF spectrometer results

The XRF spectrometer analyzed the presence of elemental impurities, in total 44 elements were considered.

According to the ICH Guidelines for elemental impurities, elements to be considered in risk assessment (if not intentionally added) for oral treatment are cadmium, lead, arsenic, mercury, cobalt, vanadium and nickel (313). A total of 216 collected samples contained cadmium. None of the others elements (lead, arsenic, mercury, cobalt, vanadium and nickel) were available. As the XFR spectrometer is a non-destructive device, the screened samples remained intact and allow “those testing positive for cadmium to be sent for confirmatory laboratory analysis” (314).

11.3.4 PharmaChk device results

The nine results of collected samples (Table 8) below reveal the contents of both APIs and are roughly comparable to results of gold standard HPLC. The deviation of artemether to HPLC

content results was maximum 5% and for lumefantrine maximum 4%. The analysis was conducted for purpose of cross-validation of the three participating laboratories.

Table 8 Preliminary results of collected samples on PharmaChk instrument

Samples	Artemether PharmaChk (spectro-photometric results)	Content of artemether determined by HPLC	Discrepancy between HPLC and spectrophoto-metric results for artemether	Lumefantrine PharmaChk (spectrophoto-metric results)	Content of lumefantrine determined by HPLC	Discrepancy between HPLC and spectrophoto-metric results for lumefantrine
HA-101	102.20%	101.24%	0.95%	102.09%	101.20%	0.88%
MA-003	100.13%	102.73%	-2.53%	101.53%	100.74%	0.78%
HA-207	104.90%	103.73%	1.13%	100.24%	100.33%	-0.09%
ZE-004	102.76%	105.01%	-2.14%	100.91%	98.61%	2.33%
BI-001	100.64%	105.78%	-4.86%	98.74%	99.12%	-0.38%
HA-219	101.98%	100.97%	1.00%	101.23%	100.09%	1.14%
CE-001	99.64%	102.57%	-2.86%	101.41%	99.82%	1.59%
KO-008	98.73%	104.29%	-5.33%	100.81%	100.12%	0.69%
HA-043	102.20%	100.96%	1.23%	101.91%	98.15%	3.83%
Ranges	98.73%-104.90%	100.96%-105.78%	-5.33%-1.13%	98.74%-102.09%	98.15%-101.20%	-0.38%-3.83%

11.4 **Confirmatory HPLC and dissolution profile results from reference laboratory**

The confirmatory testing at the Pharmanalytica SA was conducted from July-August 2017. A quarter of the collected medicine samples (75/286) were expired at the time of confirmatory HPLC analysis. Content evaluation of both APIs, degradation product analysis of lumefantrine were performed on a subset of 14 expired medicine samples which had expired two months before confirmatory analysis. Moreover the dissolution profile was assessed on a subset of 6 out of the 14 expired samples.

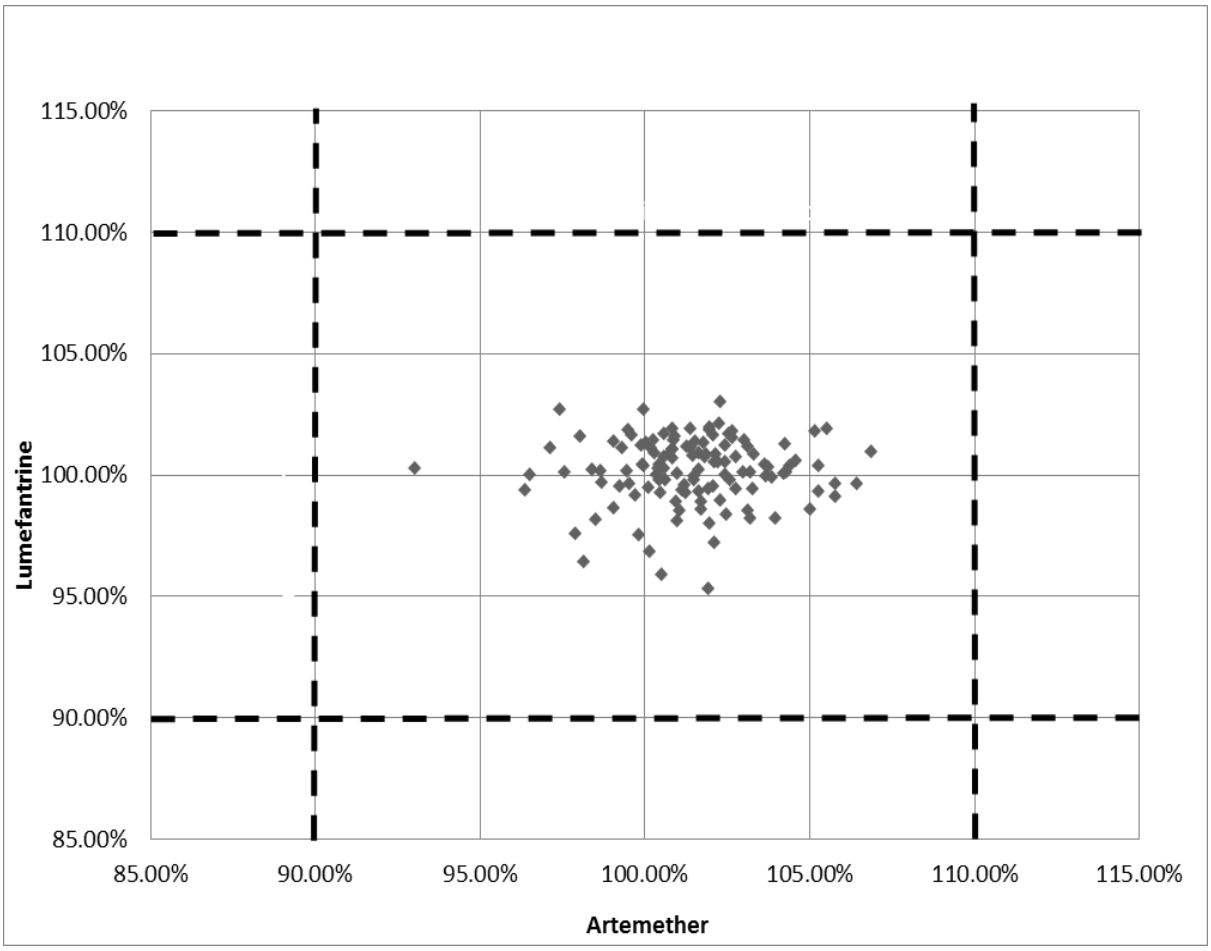
At the Locarno laboratory, packages with same batch ID sourced from the same pharmacy were defined as one individual sample, therefore the 286 collected packages of coartemether corresponded to 156 samples (included expired and nonexpired medicine samples). Content quantification of both APIs as well as degradation test of lumefantrine was conducted on a subset of 110 samples. We used Novartis HPLC monograph for testing the samples with the dosage of 20/120mg. There is no international monograph existing for coartemether combination with

40/240mg dosage, therefore the reference laboratory developed a new assay for API content evaluation of 40/240mg formulation based on the Novartis monograph for 40/280mg and considered a further dilution step.

11.5 API content evaluation

Content analysis (in percentage) of both APIs was carried out on a subset of 110 samples. API ingredients within the range of 90-110% were considered as good quality (standard) and API outside this range were defined as substandard (315). This follows the recommendations of the International Pharmacopoeia for the analysis of single-tablet samples (6). “The %API was calculated as a percent of the authentic reference tablet” (177). A subset of 110 collected samples were analyzed by HPLC in the reference laboratory in Locarno. All analyzed samples contained the stated API amounts (Figure 21) and complied with the International Pharmacopoeia requirements (6). Overall 100% (N=110) contained ≥ 90 and $\leq 110\%$ of the stated APIs and were considered of satisfactory quality for single tablet analysis (Table 10 Annex) with 95% CI (artemether): [101.09%-101.93%] and 95% CI (lumefantrine): [99.77- 100.28]. The HPLC analysis of the medicine samples at AiBST are still ongoing. The results will be published in Lancet Global Health journal (Chapter 15).

Figure 21 API% content of artemether and lumefantrine



11.6 Degradation products assessment for lumefantrine

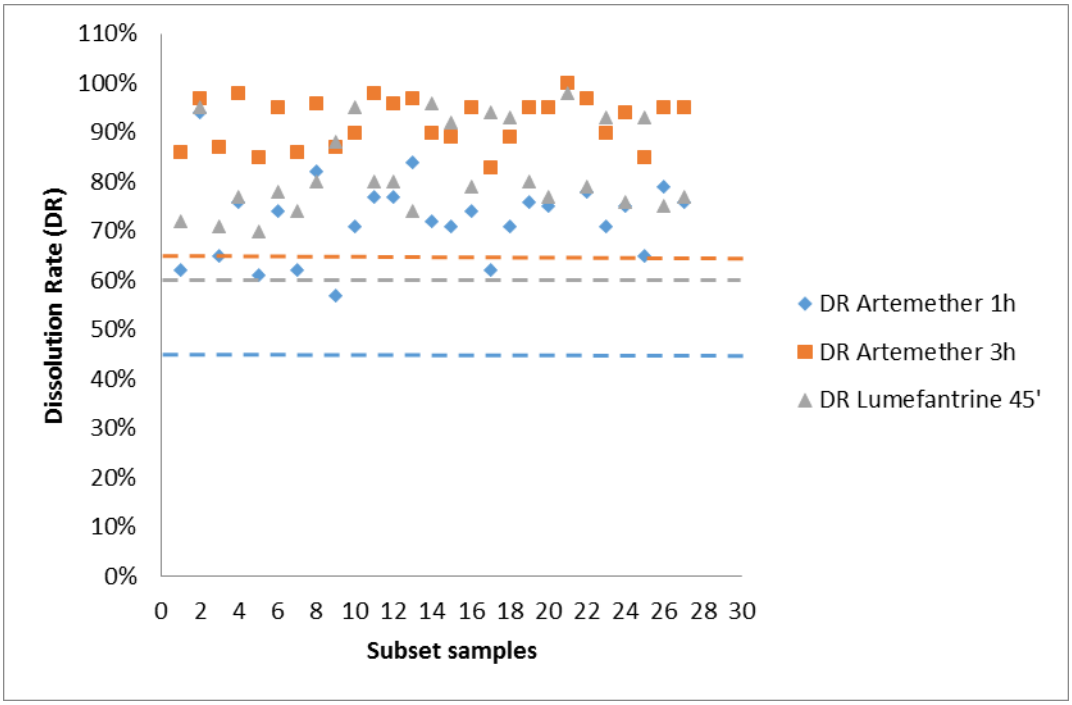
According to Novartis specifications the degradation products for lumefantrine should not exceed 0.3% of the declared content. The total impurities for lumefantrine of the analyzed subset of 110 samples were within required specifications (range <0.05%-0.21%) [Table 10 Annex].

11.7 Dissolution profile

A subset of 30 randomly selected samples of expired and unexpired products (Figure 22) was analyzed by in vitro dissolution methods and content assessment of both APIs (artemether and lumefantrine) by HPLC (282). According to Novartis in vitro dissolution testing protocols, dissolution rates (DRs) are measured at different time points. For lumefantrine after 45 minutes and for artemether after 1 and 3 hours. The DR of lumefantrine after 45 minutes analyzed by liquid

chromatography (LC) should not be less than 60% of the declared content. Dissolution of artemether analyzed by LC should not be less than 45% after 1 hour and not less than 65% of the declared content after 3 hours. 95% Confidence intervals of the dissolution rates were calculated with the Clopper-Pearson method (316) 95% CI (DR artemether 1h): [53.79-87.50]; 95% CI (DR artemether 3h): [75.95-98.67]; 95% CI (DR lumefantrine 45`): [64.42-93.91]. The DRs of all tested samples for both APIs were within specifications (Table 11 Annex).

Figure 22 DR of artemether and lumefantrine in selected samples



11.8 **Price and quality question**

The lowest average price of the sourced brands of coartemether with dosage 20/120mg was 5.50 $US and the highest 9.50 $US (Table 9) per package including 24 tablets. The unregistered brand Lonart was the most expensive on the Zimbabwean market. There is no correlation between higher price and improved quality in our study as all purchased samples were of satisfactory quality.

This is an important finding, with public health and pharmacoeconomic relevance. The following table also includes the medicinal product Komefan 280 with dosage 40/240mg which was dispensed to the covert shoppers when coartemether with dosage 20/120mg was not available.

Table 9 Price of procured medicinal brands of coartemether per package:

Trade name	Number of purchased packages	Average price in $US
Coartem®	17	8.3
Komefan	6	5.5
Komefan 280	24	7.2
Lumiter	105	6.7
Lonart	4	9.5
Lumartem	130	7.4

11.9 Discussion of Part 3

This study illustrated the use of a variety of portable, easy to operate analytical screening devices to determine the percentage of available good quality product versus substandard and falsified versions of Coartem® and its generic versions purchased from various sources (177).

To our knowledge, this was the first quality survey on the national first-line treatment of uncomplicated Plasmodium falciparum malaria (6) in Zimbabwe (101). A literature review reveals that there are only very few research projects that performed random sampling collection of medicinal products in a covert approach including all four levels of analysis: physical, package inspection, chemical, and authentication of source (101). In addition to the common qualitative screening tools Raman, NIR and XFR, we used the quantitative screening device PharmaChk which accurately determined the quantity of both APIs. Regarding the chemical analysis, we performed not only API content determination and impurities assessment, but also investigated the presence of degradation products to get more insight onto the transport and storage of the purchased pharmaceuticals. Moreorver, we evaluated the dissolution profile which conclusively determined if a product was substandard or not. In addition to the evaluation of medicines quality of collected medicines, we supported the local regulatory authority by training and establishing a laboratory of excellence through a private industry collaboration to identify substandard and falsified medicines.

In this research project we conducted a three-tiered analysis approach including visual inspection and physical testing (packaging, weight, dimensions, colour); spectrometric and fluoroscopic techniques for rapid detection of quality and quantity (Raman, NIR, XFR, PharmaChk) and confirmatory testing for identification, quantification and dissolution profile evaluation of the APIs (HPLC, dissolution tester) (177).

The screening and confirmatory assessments performed revealed that all collected samples of fixed-dose combination drug of artemether and lumefantrine were of satisfactory quality. The results from both screening tests of Raman and NIR showed that none of the collected packages were falsified. All 17 purchased packages of the original brand Coartem® passed the Raman test and 15/17 passed the NIR analysis (2 samples showed both Pass and Fail results). In total, 93% of all sourced medicinal products including Coartem® and its generic versions showed a pass in the Raman test, while 63% passed the NIR testing indicating that both APIs were available. The results from NIR and Raman indicate some disparity when comparing to HPLC results as these revealed that all collected samples were of satisfactory quality.

Both handheld spectrometer devices performed qualitative testing and were not able to accurately quantify the API content. Ultimately these two spectroscopic methods could not determine whether any of the medicinal products under test were substandard.. This is also reflected by the literature describing that both devices are not suitable for detection of SSMs (220,317). However, a limitation of this study was that the original brand Coartem® was used as the only reference for comparison of the analytical testing results for all purchased medicinal products including the generic versions. The absence of a repository of reference samples or spectra of the other five medicinal brands prevented the analysis of tablets by direct comparison (221). In particular, the consequence of this limitation came to light in the case of the sourced unregistered product Lonart. All four collected medicine packages failed both Raman and NIR tests which was due to the different pharmaceutical composition and the excipients used. In addition to the results of Raman and NIR ascertaining the presence of both APIs, the analysis of XFR revealed that there was no risk of elemental impurities.

Beyond the qualitative analysis, the screening device PharmaChk was able to specifically and accurately quantify the content of both APIs and therefore can be used to identify substandard and falsified medicines. The PharmaChk analysis yielded to comparable results with gold standard

HPLC (maximum deviation 5%). As a next step, the PharmaChk instrument needs to be evaluated for its operational accuracy and feasibility (6).

The qualitative and quantitative screening results were verified by HPLC and dissolution analysis. Confirmatory testing in the reference laboratory in Locarno determined that the content and DRs of both APIs as well as the total impurities rate of lumefantrine for the analyzed subset (range <0.05%-0.21%) were within required specifications (<0.3%). The content of artemether amounted to 96.49%-106.86% whereas the measured content for lumefantrine was 95.34%-103.02%. Overall, all collected samples contained the stated amounts of both APIs. The dissolution profile analysis of the subset of 30 samples comprised both expired and non-expired medicine samples. All 6 Komefan 280 samples showed acceptable DRs of artemether (average DR 1h:72% and 3h: 90%) and lumefantrine (DR 45`:94%) despite being three months past their expiry date at the time of analysis. This corroborates the fact that artemether and lumefantrine are inherently stable and not praticularly sensitive to heat and humidity (6). In total, all tested samples met the tolerance limits for dissolution in this study.

In addition we explored if there was a correlation between quality and price. We observed a broad price range: from $US 5.50-9.50. As all collected medicine samples were of good quality, we determined that there was no correlation between price and quality. Bate et al. observed similar finding in their study where they focused on “eight drug types on the WHO-approved medicine list from 17 LMIC countries”. The outcome of their study was that “failing drugs and non-failing generics overlap greatly in price, making it difficult to identify failing drugs based on price” (318).

Despite the satisfactory quality of the medicines under test, a number of other concerns were revealed. First, there was a level of concern on governmental medicine samples that were diverted to retail pharmacies and sold at a relatively high price. This diversion of supplies was apparent as the inscription “Not for retail sale” on the primary packaging was cut or scraped off. This illegal act may lead to limited access of this essential medicine in neighboring public hospitals and health centers (319).

Second, four of the collected samples were past their expiration date at the time of purchase (6). According to US Pharmacopoia, “the expiration date limits the time during which the article may be dispensed or used” (320). If antimalarial medicines are stored beyond their expiration date, they

may degrade (6), which may lead to “sub-therapeutic levels of the API and put the malaria patient in risk and also increase the risk of the drug-resistant parasites” (6). The US Pharmacopoeia General Notices and Requirements of this Pharmacopoeia indicates that “where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period” (321).

Third, at two collection sites, the fixed-dose combination drug of artemether and lumefantrine was dispensed in loose plastic bags excluding primary and secondary packaging and the patient information leaflet (medication package insert). The medicines name on the handwritten label indicated the innovator`s brand name whereas through visual inspection of the score of the tablet this medicinal product was unequivocally a generic version. Without the proper packaging, the medicinal products may degrade due to high temperature, moisture and light (322). Moreover, the expiry date was also not indicated on the label written by the pharmacist. The United States Pharmacopoeia General Notices and Requirements states that “the label of an official drug product…shall bear an expiration date” (321).

Fourth, in 30% of the cases (n=86), the patient information leaflet was not provided by the health care facility which leaves the patient unaware of potential side effects, contraindications and storage characteristics of the medication. Fifth, in most of the cases a label was present which included pharmacist’s instructions on how to take the medicine, however there was a great discrepancy within respect to level of detail. Moreover in 23/283 cases, the expiration date on the label did not correspond to the one on the primary and secondary packaging. In most of these cases the handwritten expiration date by the pharmacist on the packaging was significantly longer than those in the official packaging material. This presents considerable concern since it is known as described above that the medicinal product stored beyond expiration date may degrade and therefore can lead to subtherapeutic levels of API and potentially put the malaria patient at risk (6). In the United States Pharmacopoia General Notices and Requirements of this Pharmacopoeia the term “beyond-use date” is defined as “the date after which an article must not be used. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-

dose container or the expiration date on the manufacturer`s container, whichever is earlier, unless stability data or the manufacturer`s labeling indicates otherwise" (321).

In this pilot study we applied a mixed approach using random and convenience sampling. We noticed limited access of coartemether combination medicines despite prevailing peak malaria season in the private sector during the first collection round where we used covert random sampling approach in the 17 targeted cities throughout Zimbabwe. Thus we would need a random sample size (n) of at least 151. This meant that procurement from at least 151 different outlets selling coartemether medicines would be required to obtain an objective estimate of the prevalence of those selling substandard and/or falsified coartemether drugs at one time point in Zimbabwe (11).

Zimbabwe has a broad estimated prevalence range of 11-44%. Based on the assumption of the estimated prevalence of 11% and the sample size calculation result, we needed to collect samples from 151 outlets to obtain an objective estimate of the prevalence of outlets selling substandard and/or falsified coartemether medicines at one time point in Zimbabwe. We visited 200 sites from the public sector if we combine the number of samples applying random and convenience sampling. Unfortunately, we could not visit the required 314 outlets (assumption prevalence of substandard medicines and counterfeit medicines in Zimbabwe is 28.5%) based on a random sampling approach. We were only able to acquire 76 packs of medicines by random sampling collection from 86 visited sites of the private sector including retail and hospital pharmacies and informal drug outlets.

In the subsequent sample collection in March 2017, we applied convenience sampling which enabled the purchase of 210 medicinal packages from 114 drug outlets in one week, a threefold increase of the number of samples. This is presumably one more reason why most of the medicine quality surveys apply convenience sampling. Moreover, among the six registered brands, only four (Coartem®, Lumiter, Lumartem, Komefan) were available at the selected sites. In addition, at two pharmacies, four medicinal packages of a generic unregistered brand (Lonart) was sold, which is also not WHO-prequalified. This is alarming and contravenes against the recommendations of the WHO Expert Committee emphasizing to drug regulatory authorities to only purchase medicines from prequalified manufacturers (323). With regards to the informal market situation of this country, illicit outlets were available in some of the targeted cities including Harare, Shamva,

Kadoma, Buhera and Murehwa. No antimalarials were sold, but medicines for erectile dysfunction, antibiotics, painkillers and skin-whitening creams were all available.

Our study had a number of limitations (6). Although we did not reach the required sample size in this pilot study to obtain a prevalence estimate of antimalarial drug quality (282), we considered it was ethically unacceptable (6) to carry out a third sample collection round. Since it was peak malaria season from January to April in Zimbabwe, we did not want to exacerbate the limited access to this essential medicine. Moreover, this study was only conducted in the private sector and not in public health facilities where the scale of the problem of expired and substandard drug remains unknown and deserves attention (6). Indeed, it would also be interesting to assess if there are higher rate of SSMs in the public sector due to the cheaper prices. Finally, this pilot study "only produced a snapshot in time and only reports on the quality of" artemether lumefantrine with dosage 20/120mg.

We recognized various challenges when planning and conducting the field study on quality of antimalarials in Zimbabwe. One of the challenges was, despite guidelines from WHO (324) and researchers (11) on the subject of the quality of medicines, it is not clear what is the most suitable approach for procuring medicine samples for the analysis of drug quality [random sampling or lot quality assurance sampling (LQAS)] (6). Moreover, there is no single accepted range for defining medicine samples as being good quality in terms of %API (6). While the International Pharmacopoeia requires for assay of tablets 90-110% of API content of the label claim (325), "the ICH and USP recommend that the percentage concentration of API should fall within 80% - 120%" (326).

There are several guidance documents required for the conduct of field studies for medicines quality evaluation. These include instructions for procurement of medicinal samples, sample analysis guidelines and reporting guidelines. There is a necessity of a standard methodological approach to assessment of medicines quality [with not only the focus on falsified medicines (e.g. WHO Draft guidance on testing of "suspect" falsified medicines (231) or Council of Europe: Testing of counterfeit/illegal medicines (232)] including all relevant instructions and recommendations in order to guarantee that the results of these field studies are valid and robust to enable decision making and development of policies by regulators.

12 Conclusion of Part 3

In the quality medicine pilot study carried out here, no suspected falsified and/or substandard samples of coartemether were identified in the private health sector in Zimbabwe. The results of both qualitative and quantitative screening methods were corroborated by confirmatory analysis revealing that all collected samples of coartemether were of satisfactory quality. However, the presence of diverted medicinal products from public into private health care facilities as well as the availability of antimalarial drug that are outside of national policy and guidelines warrant further investigation by the local regulatory authority.

This study showed that the quantitative screening tool PharmaChk device is ready for testing under field conditions. The implementation of this device, which can be continuously used in the field by drug inspectors, law enforcement officials, and pharmacists, is required to quickly assess whether medicines are substandard or falsified (6). As issues of poor quality medicines do not only affect antimalarial medicines, further research should be conducted to assess medication for treatment of other diseases focusing on treatment of conditions associated with high mortality and high morbidity.

Global collaboration is required to combat the increasing threat of substandard and falsified medicines. This research project showed the successful research collaboration of non-private and private institutions on capacity building in the field of quality of medicines (101).

13 Final discussion and outlook

The topic of SSMs is a multifaceted and largely neglected problem (28,327). Since 1988 “falsified medicines have achieved most attention” (6). Most of the studies performed until now did not differentiate between falsified and SSMs (14). Although SSMs show greatest prevalence in developing countries (328), the increase in number of medicine recalls in UK and Portugal (8,55) and cases of malaria resistances in UK (329,330) highlight the omnipresence of this burden. SSMs still cause thousands of adverse reactions and some deaths (331) and are a substantial threat to public health. Due to lack of clarification on the definition of SSMs and description of its multiple categories (Figure 2) as well as the presence of only few prevalence studies of SSMs, the true extent of the problem is not well documented. Strategic QC testing is a cornerstone of the mechanisms in place to protect against substandard medicinal products (332). Most field studies were performed with antimicrobials, but only few on non-communicable diseases such as diabetes, cancer etc. (101).

Due to the different causes why SSMs may arise (12), the detection of SSMs is a big challenge and requires a strong global post-marketing surveillance and inspection system as well as routine QC (23). Hence, the detection of SSMs essential and requires particular attention. In my research I focused on the development of two innovative detection approaches and validated these in a field study in Zimbabwe.

Part 1 of this thesis described the effective approach of analyzing the pharmacovigilance database Vigibase® with disproportionality statistics to support the detection of SSMs. This detection tool can be characterized as time-, resource and cost-efficient. This approach can be applied worldwide to facilitate the selection process of medicines for quality testing in field surveys. The greatest disadvantage of all available pharmacovigilance databases and registries is the quality and relatively limited numbers of available reports, due to under-reporting (170). All these data sources have a common problem in that most occurrences are “probably unreported, reported to the wrong agencies, or kept confidential” (98). There is a paucity of data in the field of established medicines (Chapter 10.1). The study on Vigibase® (Chapter 8) revealed that common data sources on ICSRs in pharmacovigilance databases contain mostly generic names but a more limited data set with full trade names. This aggravates the detection of SSMs as there could be various trade names either

registered or unlicensed pharmaceuticals behind each of the generic names and increase the risk of duplication of cases (Chapter 8). In addition, there is no presence of physical samples of the suspected medicinal products which impedes clearing up the cases by conducting secondary research including analytical testing.

The implementation of MedDRA® version 19.0 in March 2016 deployed a new (27th) System Organ Class (SOC) called 'Product Issues' update on the 27th SOC Product issues (333). This will increase the capability of explicit coding of ICSRs associated with medicinal products, as well as improving retrievals and outputs related to terms describing such events. In the future the pharmaceutical industry and regulatory authorities should collaborate with the MedDRA® MSSO to develop a standardized MedDRA® query (SMQ) for SSMs. This standardized list could comprise a core or narrow list specific to characteristic features caused by SSMs. Beyond this would be an extended or broad group of terms which would increase the retrieval of ICSR potentially associated with SSMs, and other issues with product quality; devices, manufacturing and quality systems; supply and distribution and falsified medicinal products. Existing PTs/Lowest Level Terms (LLTs) will be moved to more specific groupings and new manufacturing and quality system terms will be added. In future mining analyses these fundamental changes to assess the feasibility of revealing more tightly defined and precise clusters indicative of potential SSMs shall further be considered. In order to improve the performance of the developed algorithm there should be continued efforts to work with the MedDRA® MSSO to refine and extend the new SOC with the goal of extending the utility by providing the capability to conduct research for product-specific issues.

Part 2 of the thesis outlined the state of the art of analytical technologies used for identification of SSMs with particular focus on the PharmaChk device. Currently this is the only existing instrument which unifies the abilities of identifying and accurately quantifying APIs as well as their dissolution profile (28). For the first time a fixed-combination medicine of two pharmaceutical compounds (artemether and lumefantrine) was tested on the PharmaChk device. Thus part 3 of this thesis showed the successful implementation of the Coartem® assay on the PharmaChk device by using medicinal field samples of Coartem® and its generic versions collected from various healthcare facilities in Zimbabwe. We showed that the application of PharmaChk device as a

portable screening tool can provide rapid assessment of medicines quality for SF medicines. This analytical technology showed comparable results (maximum 5% deviation) to the gold standard method (HPLC).

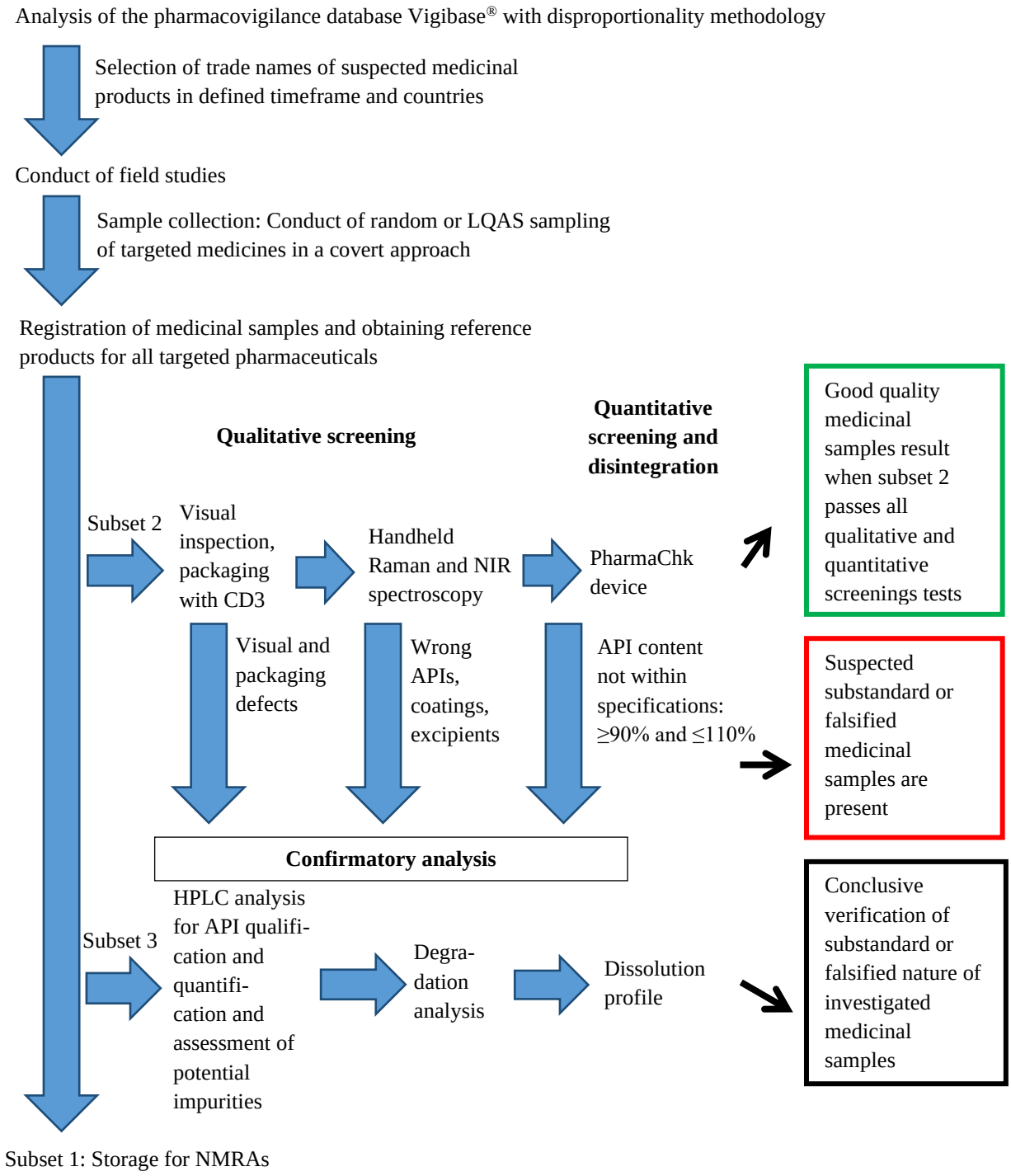
However, this device proved to have some limitations during its application in the research project in Zimbabwe and certain challenges must be addressed (28). The PharmaChk technique needs to be tested in more field surveys to prove its field feasibility. Moreover, the reference library needs to be developed similar to the libraries available in the handheld Raman and NIR spectrometers so that calibration with the reference substance is not required anymore. In addition, if the range of the International Pharmacopoeia for assay of tablets 90-110% of API content is considered and as an example the PharmaChk instrument assesses a content of 90% API content including systematic error of ±5%, there is a risk that the device evaluates the medicinal sample as good quality although it is substandard and leads to a false negative result (type II error). Further research and development of this instrument to increase the device's sensitivity is pivotal to achieve accurate differentiation between good quality and substandard medicinal products. For now PharmaChk can describe the quantity of the API and the dissolution profile, thus in future it might also be possible to assess the presence of contaminants and known degradation products. This device will not be able to replace confirmatory testing with HPLC or MS as these technologies unequivocally confirm the substandard nature of medicinal products (206). In the future this instrument may triage samples for medicines' quality confirmatory analysis and reduce time and analysis costs in developing countries .

A thorough reflection of the current situation to identify SSMs reveals that analytical "…technologies alone will not solve the problem…" (26). The conduct of representative and generalizable studies in the field would be beneficial (52) adding to the concerted efforts of regulators, the pharmaceutical industry, and enforcement agencies to implement worldwide regulatory and general manufacturing standards. There is no established threshold for defining medicines as being substandard in terms of %API (6), DRs and impurities rate. Moreover, there is a definite need for structured and standardized guidance on medicines quality and assessment of SSMs (332).

Both screening methods presented in this thesis may support various stakeholders to combat the problem of SSMs. The pharmacovigilance tool can be employed by MOHs, the pharmaceutical industry and NGOs whereas the PharmaChk device can also be applied by HCPs in hospitals and pharmacies, importers, drug inspectors, law enforcement officers, border officials and manufacturers. Both tools can be successfully used to triage suspected substandard or falsified medicine samples for further verification analysis. The triage process allows saving analysis costs and the testing of large quantities of medicine samples throughout the whole supply chain. Confirmatory analysis determines the type of substandard nature of the medicinal samples which can be either due to degradation, contamination or bioavailability issues. Based on the investigations made, sanctions and policies can be established in a shorter timeframe. These detection approaches are both easy to operate, cheap and quick methods to be implemented worldwide for detection and monitoring of quality of medicines which can be either based on WHO Medical product alerts (95) or for regular inspection of the pharmaceutical market. Both detection methods require a repository of reference samples or spectra to perform analysis of tablets by direct comparison (221).

Based on the application of both detection tools in the research study in Zimbabwe, we constructed a roadmap (Figure 23) for the efficient assessment of quality of medicines in field surveys (11). This roadmap presents the effective combination of both presented detection methods. We incorporated the testing procedures of suspect SSFFC medicine samples recommended by WHO (206) together with the procedures used to investigate malarial drug quality in developing countries by CODFIN (11). It is notable that each of the steps mentioned below should be performed in accordance with WHO guidelines for sample collection and reporting (206) and the recommendations of the MEDQUARG checklist (11).

Figure 23 Suggested roadmap for field surveys on quality of medicines



The pharmacovigilance approach, using disproportionate analysis on ICSRs in Vigibase®, which was validated for the first time in this research project, allows the targeting of countries and trade names of medicinal products including a higher probability of finding SSMs. In addition to

Vigibase® other pharmacovigilance databases and/or registries could be employed (e.g. mobile app developed in WEB-RADR project). The WEB-RADR project which was launched in 2014, is based on a public-private partnership by Novartis and the MHRA (334) developed a mobile app for HCPs and the public to report suspected ADRs (335).

After selecting the countries and trade names, field studies in developed and developing countries shall be conducted by using a suitable sample collection method. For all selected trade names, reference samples need to be provided by the manufacturers. Every collected medicinal sample will be registered in a database and thereafter divided into three subsets. Subset 1 will be stored by NMRA (in case further investigation analysis is required). Subset 2 is used for qualitative and quantitative screening purpose. Qualitative screening analysis include visual inspection [following WHO Checklist for visual inspection of packaging (336)], CD3 analysis of the packaging and Raman and NIR spectrometry for evaluating the chemical composition of the API and the excipients. Qualitative screening tests include content evaluation in %API with the PharmaChk device. If subset 2 passes all screening tests, this indicates that the medicinal sample is of satisfactory quality. But if one of the analysis tests reveals different results compared to the reference product then this represents a suspected case and needs to be further investigated by confirmatory analysis. Verification testing includes qualitative and quantitative assessment of API and impurities in order to determine if there was a manufacturing problem. Moreover degradation analysis is required to reveal if the medicine sample was stored adequately. For conclusive evaluation of the substandard nature of subset 3, the bioavailability of the sample needs to be analyzed with the dissolution test.

Overall, we approached the subject of SSMs holistically. The research started with pharmacovigilance, progressed on to analytical approaches to identify SSMs and the learnings were applied in a field setting in Zimbabwe (Chapter 10). We also considered other domains to assess management of the problems associated with SSMs. These included monitoring of medicines quality based on AE reports, rising awareness on burden of SSMs, capacity building of the national laboratory in Zimbabwe including provision of training on qualitative and quantitative analysis of SF samples as well as building various relationships with academia, the pharmaceutical industry, analytical laboratories and the WHO to extend the current knowledge on detection of

SSMs.

In addition to pharmaceutical industry and healthcare systems, quality evaluation and control are also featuring in food and aviation industries (337) from which a significant learnings can be leveraged for addressing the SSMs issues. Indeed, both domains are relevant, due to potential safety concerns and careful controls (338). Checklists (339) and full adherence to national and cross-border quality standards (340) characterize their processes. Amir Attaran, professor in the faculties of law and medicine at the University of Ottawa (341), who has done extensive research on the field of defective medicines, said in a recent interview concerning aviation quality regulations:

"There are dozens of treaties on civil aviation, and every single country is following those. If not, they don`t fly" (337).

In the food industry, traceability practices are the norm and have been successfully maintained over periods of years (342). Since 2002, the European Union`s General Food law (Regulation 178/2002, Article 18) requires compulsory traceability for food and feed operators (343).

Compared to the food law, the EU Commission issued the EU Falsified Medicines Directive (EU FMD) only in 2013 which includes serialization, verification and compliance reporting requirements (344). Notably "this legislation introduces track and trace regulations that enable harmonized, European-wide measures to rigorously control the safety and supply of medicines for human use" (344). All pharmaceutical manufacturers, parallel importers, wholesalers and pharmacies have to comply from February 9, 2019 (344). According to the update on the implementation of the medicine traceability there are some drawbacks (345). Currently the setup of the repository systems which are essential to verify the authenticity of medicines is behind schedule. Moreover there are 17 pending contract agreements, issues with stakeholder integrations and lack of appropriate hospital budget plans covering the necessary equipment and resources costs for implementation of the new legislation in public hospitals (345).

Thus, in regard to medicine quality, we do not need to reinvent the wheel. But we do need to learn lessons, and learn them quickly, to apply effective measures to prevent this scourge from impacting healthcare systems across the world.

13.1 Future directions of the research projects described above

Ongoing and future work towards addressing new detection approaches for identifying SSMs are outlined below:

• We are currently looking at the implementation of an additional quantitative screening tool which can be used in field surveys by drug inspectors and law enforcement officials to rapidly assess whether medicines are of good quality, substandard or falsified (6).

• A follow-up project is planned in Zimbabwe to extend on other disease areas including non-communicative diseases as well as in other countries in Africa.

• There is common interest with WHO Essential Medicines and Health Products (EMP) department (346) to understand which AEs reported in Vigibase® can be related to SSMs. We would like to assess if there are more preferred terms indicative of SSMs.

14 Overall conclusion

The aim of this research was to explore detection approaches for identifying SSMs. We described the effective approach of analyzing the pharmacovigilance database Vigibase® with disproportionality methodology to support the detection of SSMs. We showed that the application of PharmaChk device as a portable analytical screening tool can provide rapid assessment on evaluation of medicines quality for substandard and falsified medicines. The field study in Zimbabwe showed the successful implementation of the Coartem® assay on the PharmaChk device by using medicinal field samples of Coartem® and its generic versions collected from various private healthcare facilities. These detection approaches can be used by concerned stakeholders to fill the current gaps regarding detection of SSMs in the healthcare system. The pharmacovigilance detection approach can be employed by Ministries of Health, the pharmaceutical industry and the

NGOs whereas the PharmaChk instrument can moreover be applied by HCPs in hospitals and pharmacies, importers, drug inspectors, law enforcement officers and border officials. In addition we developed a roadmap that synthesizes both detection methods together with the procedures used to investigate medicines drug quality in field studies.
My hope is that this research will stimulate further thoughts and potentially activity by various stakeholders to improve the current status, and to enhance research activities on SSMs.

15 Publications

The work detailed in Chapters 9 and 10 are currently under internal review for separate publications. The research project described in Chapter 12 was conditionally accepted for submission in Lancet Global Health journal.

I would like to end my PhD thesis with the words of James Fitzgerald, Director of the Department of Health and Services: “Quality medicines are essential to provide quality health care. We cannot take for granted that all medicines meet international standards in quality, safety and efficacy. We must remain vigilant all times, and put in place the necessary safeguards to protect people within our health systems.”

16 Appendix

Table 10 Annex table of the subset content analysis of 110 samples of artemether and lumefantrine as well as total impurities rate of lumefantrine

Sample number	Assay Artemether	Assay Lumefantrine	Degradation products for lumefantrine: Total impurities
ZW_2017_001	99.70%	99.19%	0.05%
ZW_2017_003	102.74%	99.43%	<0.05%
ZW_2017_005	102.04%	99.54%	<0.05%
ZW_2017_006	100.36%	100.05%	<0.05%
ZW_2017_007	96.34%	99.38%	0.16%
ZW_2017_008	98.68%	99.70%	0.05%
ZW_2017_009	100.08%	99.48%	0.10%
ZW_2017_010	101.48%	99.83%	<0.05%
ZW_2017_012	102.64%	101.81%	<0.05%
ZW_2017_013	100.83%	101.08%	<0.05%
ZW_2017_014	101.68%	98.90%	0.05%
ZW_2017_015	100.26%	100.90%	0.05%
ZW_2017_016	99.48%	101.88%	<0.05%
ZW_2017_017	98.48%	98.20%	0.06%
ZW_2017_018	96.49%	100.05%	0.06%
ZW_2017_019	103.96%	98.23%	<0.05%
ZW_2017_020	97.88%	97.58%	0.05%
ZW_2017_021	100.96%	98.15%	0.06%
ZW_2017_022	98.12%	96.44%	0.06%
ZW_2017_023	102.42%	100.53%	<0.05%
ZW_2017_024	101.62%	100.26%	<0.05%
ZW_2017_025	99.81%	97.54%	0.06%
ZW_2017_028	100.86%	101.47%	<0.05%
ZW_2017_029	100.35%	100.02%	0.05%
ZW_2017_031	101.96%	98.04%	0.05%
ZW_2017_032	101.53%	101.41%	<0.05%
ZW_2017_033	102.42%	100.04%	<0.05%
ZW_2017_034	99.96%	102.70%	<0.05%

Sample number	Assay Artemether	Assay Lumefantrine	Degradation products for lumefantrine: Total impurities
ZW_2017_035	102.09%	100.56%	<0.05%
ZW_2017_036	101.17%	99.61%	<0.05%
ZW_2017_037	100.82%	100.69%	<0.05%
ZW_2017_039	99.23%	99.54%	<0.05%
ZW_2017_040	101.61%	100.94%	0.05%
ZW_2017_041	99.60%	101.64%	<0.05%
ZW_2017_042	100.62%	99.84%	<0.05%
ZW_2017_043	100.56%	100.31%	<0.05%
ZW_2017_044	102.14%	100.86%	<0.05%
ZW_2017_045	99.03%	101.40%	<0.05%
ZW_2017_047	100.71%	100.89%	<0.05%
ZW_2017_048	100.43%	99.84%	<0.05%
ZW_2017_051	101.24%	101.20%	<0.05%
ZW_2017_052	101.11%	99.40%	<0.05%
ZW_2017_055	101.63%	99.33%	0.05%
ZW_2017_057	101.22%	99.29%	<0.05%
ZW_2017_058	103.12%	98.57%	<0.05%
ZW_2017_059	100.92%	98.94%	0.06%
ZW_2017_060	100.12%	96.84%	0.06%
ZW_2017_061	99.91%	100.46%	0.06%
ZW_2017_062	102.46%	98.41%	0.05%
ZW_2017_063	101.91%	95.34%	0.10%
ZW_2017_064	102.52%	101.71%	<0.05%
ZW_2017_065	101.69%	98.61%	0.17%
ZW_2017_066	103.19%	100.11%	0.06%
ZW_2017_067	102.24%	102.13%	0.07%
ZW_2017_068	105.14%	101.82%	<0.05%
ZW_2017_070	102.08%	97.21%	<0.05%
ZW_2017_072	103.19%	98.25%	<0.05%
ZW_2017_073	98.03%	101.59%	0.05%
ZW_2017_074	102.29%	103.02%	<0.05%
ZW_2017_075	100.46%	99.30%	0.05%
ZW_2017_076	106.86%	100.99%	<0.05%

Sample number	Assay Artemether	Assay Lumefantrine	Degradation products for lumefantrine: Total impurities
ZW_2017_077	102.99%	101.46%	<0.05%
ZW_2017_078	102.65%	101.58%	<0.05%
ZW_2017_079	99.44%	100.21%	<0.05%
ZW_2017_081	101.82%	100.74%	0.05%
ZW_2017_083	101.43%	100.81%	<0.05%
ZW_2017_085	103.29%	100.86%	<0.05%
ZW_2017_086	102.43%	101.23%	<0.05%
ZW_2017_087	100.40%	100.30%	<0.05%
ZW_2017_088	101.77%	101.35%	<0.05%
ZW_2017_089	97.12%	101.12%	0.05%
ZW_2017_091	100.23%	101.44%	<0.05%
ZW_2017_092	100.90%	101.61%	<0.05%
ZW_2017_093	99.04%	98.66%	0.06%
ZW_2017_094	101.47%	99.99%	<0.05%
ZW_2017_095	99.94%	100.39%	<0.05%
ZW_2017_096	99.51%	99.64%	<0.05%
ZW_2017_100	99.28%	101.13%	<0.05%
ZW_2017_101	101.84%	100.86%	<0.05%
ZW_2017_102	100.56%	100.79%	<0.05%
ZW_2017_103	103.26%	99.46%	0.06%
ZW_2017_104	104.24%	101.29%	<0.05%
ZW_2017_105	103.63%	100.47%	<0.05%
ZW_2017_107	99.88%	101.22%	0.05%
ZW_2017_108	102.26%	98.95%	0.05%
ZW_2017_109	105.75%	99.65%	<0.05%
ZW_2017_110	105.27%	100.42%	<0.05%
ZW_2017_111	103.73%	100.33%	0.05%
ZW_2017_113	104.40%	100.40%	<0.05%
ZW_2017_116	103.64%	100.00%	<0.05%
ZW_2017_118	100.97%	100.09%	0.06%
ZW_2017_119	104.56%	100.60%	<0.05%
ZW_2017_120	103.83%	99.94%	<0.05%
ZW_2017_122	105.51%	101.92%	<0.05%

Sample number	Assay Artemether	Assay Lumefantrine	Degradation products for lumefantrine: Total impurities
ZW_2017_123	104.19%	100.07%	<0.05%
ZW_2017_125	102.73%	100.74%	<0.05%
ZW_2017_127	97.56%	100.14%	0.16%
ZW_2017_129	101.92%	99.43%	<0.05%
ZW_2017_130	105.78%	99.12%	<0.05%
ZW_2017_134	100.51%	95.90%	0.21%
ZW_2017_137	105.25%	99.33%	<0.05%
ZW_2017_138	104.29%	100.12%	<0.05%
ZW_2017_141	105.01%	98.61%	<0.05%
ZW_2017_142	93.00%	100.27%	0.19%
ZW_2017_143	102.57%	99.82%	<0.05%
ZW_2017_145	102.97%	100.11%	<0.05%
ZW_2017_146	102.19%	100.56%	<0.05%
ZW_2017_148	101.03%	98.56%	0.10%
ZW_2017_149	100.82%	101.07%	<0.05%
ZW_2017_153	106.41%	99.67%	<0.05%
Mean	**101.51%**	**100.03%**	

Table 11 Artemether and lumefantrine dissolution rates of 30 samples at 1h, 3h and 45`

Subset analysis	DR Artemether 1h	DR Artemether 3h	DR Lumefantrine 45'
ZW_2017_001	62%	86%	72%
ZW_2017_007	94%	97%	95%
ZW_2017_010	65%	87%	71%
ZW_2017_013	76%	98%	77%
ZW_2017_015	61%	85%	70%
ZW_2017_019	74%	95%	78%
ZW_2017_022	62%	86%	74%
ZW_2017_031	82%	96%	80%
ZW_2017_032	57%	87%	88%
ZW_2017_038	71%	90%	95%
ZW_2017_047	77%	98%	80%

Subset analysis	DR Artemether 1h	DR Artemether 3h	DR Lumefantrine 45'
ZW_2017_052	77%	96%	80%
ZW_2017_081	84%	97%	74%
ZW_2017_093	67%	90%	74%
ZW_2017_097	73%	91%	92%
ZW_2017_107	64%	86%	76%
ZW_2017_117	72%	90%	96%
ZW_2017_124	71%	89%	92%
ZW_2017_125	74%	95%	79%
ZW_2017_127	62%	83%	94%
ZW_2017_128	71%	89%	93%
ZW_2017_129	76%	95%	80%
ZW_2017_130	75%	95%	77%
ZW_2017_134	100%	100%	98%
ZW_2017_137	78%	97%	79%
ZW_2017_140	71%	90%	93%
ZW_2017_141	75%	94%	76%
ZW_2017_142	65%	85%	93%
ZW_2017_143	79%	95%	75%
ZW_2017_153	76%	95%	77%
Mean	**73,03%**	**91,9%**	**82,6%**

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