Evaluation of glibenclamide quality and stakeholders' perception of medicine quality in the clinical settings of the Ministry of Interior in Saudi Arabia

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Abstract

Aim: To explore medicine quality and perception among the stakeholders in the Ministry of Interior Medical Services (MOI-MSD) clinical settings in Saudi Arabia using glibenclamide as an indicator.

Method: A mixed method approach was used in two phases. Phase one involved chemical analysis for identity and quantity of the active pharmaceutical ingredient (API), visual analysis and authentication of source of a popular diabetes medicine (glibenclamide) collected from MOI-MSD general warehouse in Riyadh, Saudi Arabia. Phase two contained a focus group discussion, self-completed survey questionnaires and semi-structured interviews to explore the perceptions of various stakeholders including commissioners, physicians, pharmacists and patients in the MOI-MSD settings in Saudi Arabia about medicine quality and related problems.

Data analysis: Phase one collected quantitative data of API quantity from the chemical analysis of glibenclamide samples using a high performance liquid chromatography apparatus (HPLC) based on United States Pharmacopoeia (USP 36) method. The visual inspection of glibenclamide samples was performed using tool kit developed by The World Health Professions Alliance (WHPA) and The International Pharmaceutical Federation (FIP). The authentication of glibenclamide source was performed by on-site comparison of available samples in the general MOI-MSD warehouse with the available official reception documents. Phase two collected quantitative and qualitative data regarding perceptions about medicine quality and related problems and subsequently analysed them using SPSS for descriptive statistics and NVivo version 10 for thematic analysis following data coding and the development of themes and sub-themes. Subsequently, stakeholders' data were triangulated to establish common and specific themes and sub-themes among MOI-MSD stakeholders.

Findings: Phase one of the study found that all glibenclamide samples were within acceptable USP limits in terms of identity and quantity between 90-110%. It was also found that all available glibenclamide batch numbers were present in the official reception documents and the visual analysis of samples revealed no visible errors on the

medicine samples or its packaging. Phase two of the study found that most stakeholders, particularly commissioners and physicians, believed that medicine quality was good or excellent in Saudi Arabia. However, the commissioners, physicians and pharmacists believed that the quality of medicines in the MOI-MSD was less than what is available in Saudi Arabia but patients mostly disagreed with these views. Most patients believed that the quality of medicines was high in both the Saudi Arabian market and in the MOI-MSD settings. Limited knowledge about good quality medicines and counterfeit medicines was found among most stakeholders where the quality of medicines was commonly associated with the effect rather than technical attributes of medicines including content, appearance and source. The stakeholders in this study reported a wide range of behaviour when in doubt about medicine quality such as reporting these doubts to authorities, finding alternative medicines, stopping the medicine use and taking no further action regarding these doubts. Furthermore, all stakeholders have identified medicine procurement focusing on price rather than quality, difficulty in reporting medicine quality problems and medicine storage conditions as challenges to medicine quality in the MOI-MSD. Patients, particularly chronic patients from Jeddah city, have complained about medicine non-availability in their local MOI-MSD primary clinic and expensive medicine prices.

Conclusions: Glibenclamide quality in the MOI-MSD settings was found to be acceptable in terms of API identity and quantity, source and visual appearance. The perception about medicine quality in these settings seems to be low particularly from commissioners and pharmacists but not the patients. There is an urgent need to implement quality assurance steps to increase the commissioners and pharmacists trust in the quality of their medicines at the medicine selection, procurement, storage and transportation stages in addition to improving the accessibility to report medicine quality problems to all stakeholders. Subsequently, future research is needed to measure and evaluate the impact of these quality assurance steps on the confidence of commissioners and pharmacists trust in the quality of the MOI-MSD medicines. Furthermore, patients' issues about medicine non-availability need to be addressed rapidly as it could result in patients' acquiring medicines from unknown sources and/or cause additional financial burdens.

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List of abbreviations

WHO	World Health Organisation
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
OOS	Out of specification
FDA	Food and Drug Administration
SSFFC	Substandard/Spurious/Falsely-labeled/Falsified/Counterfeit medicines
GMP	Good Manufacturing Practices
API	Active pharmaceutical ingredients
TB	Tuberculosis
USA	United States of America
PSI	Pharmaceutical Security Institute
TLC	Thin layer chromatography
NIR	Near-infrared
HPLC	High Performance Liquid Chromatography
UV	Ultraviolet
MS	Mass Spectrometer
LC-MS	Liquid Chromatography-Mass Spectrometry
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
WHPA	World Health Professions Alliance
FIP	The International Pharmaceutical Federation
INN	International Non-Proprietary Name
NTI	Narrow Therapeutic Index
CDSI	The Central Department of Statistics and Information
MOH	Ministry of Health
MOE	Ministry of Education
MODA	Ministry of Defense
MOI	Ministry of Interior
NGH	National Guard Healthcare
SFDA	The Saudi Food and Drug Authority
NUPCO	The National Unified Procurement Company for Medical Supplies
GPP	Group Purchasing Program for the Gulf Countries

MOI-MSD	Ministry of Interior Medical Services Department
MOI-PCC	Ministry of Interior primary care clinics
NR	Not reported
USP	United States Pharmacopeia
UK	United Kingdom
NCD	Noncommunicable disease
UAE	United Arab Emirates
NSAID	Nonsteroidal anti-inflammatory drugs
CV	Cardiovascular
KSA	Kingdom of Saudi Arabia
RS	Relative standard
RPM	Rounds per minute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
GP	General Practitioner
ECDA	Ethics committee at the University of Hertfordshire
SD	Standard Deviation
UH	University of Hertfordshire
Vs.	Versus
NICE	The National Institute for Health and Care Excellence
CI	Confidence interval

1 Chapter 1: Introduction

1.1 History of medicine quality and related problems

Concerns about medicine quality can be traced back to the innovation of the medicines themselves. Warning writings about adulterated medicines were found in the 4th Century BC. Dioscorides identified such dubious medicines and advised on their detection in the 1st Century AD (WHO, 1999a). Cases of fake cinchona bark and quinine were reported in the 19th Century (Newton, Green & Fernandez, 2010; Clift, 2010). In more recent times, concerns about medicine quality resurfaced in 1951 briefly following the establishment of the World Health Organisation (WHO) in 1948. Consequently, the WHO adapted Resolution EB7.R.79 to establish methods that unify the control of medicines on a global scale in order to facilitate health and commercial requirements (WHO, 1999a). In the 20th Century AD, further international attention has been focused on fake medicines. The International Medical Products Anti-Counterfeiting Taskforce (IMPACT) was established following the WHO meeting in Rome in 2006 (WHO, 2011; Edwards, 2011; WHO, 2012a). The aim of IMPACT was to combat the trade in fake medicines by combining the efforts of health regulatory agencies, international organisations, pharmaceutical companies, healthcare professionals and law enforcement experts (Edwards, 2011). However, some countries were sceptical of IMPACT's role and duties, as it was perceived as a waste of scarce resources. Such opinions concluded that resources should be allocated towards combatting other more serious health-related threats from narcotics or the tobacco industry (IMPACT, 2011). The limited availability of up to date information about IMPACT's current role, activities and cooperation with governmental agencies in the public domain does not allow for any estimation of attitude change towards IMPACT nor does it allow for evaluation of its success.

1.2 Definition and views about medicine quality and related problems

It is widely accepted that a high quality medicine is defined in terms of fulfillment of technical pharmacopoeial specification concerned with the medicine's identity, purity, potency, dosage form uniformity, bioavailability and stability (Quick, Rankin, Liang & O'Connor, 1997; Patel, Norris, Gauld & Rades, 2009). According to the WHO,

standards of medicine quality would also include that the medicine is effective without severe side effects and maintains its appearance and therapeutic ability throughout its claimed shelf life (WHO, 1997). A high quality medicine should also be registered with healthcare regulators in the intended market and have a correct label that clearly identifies the name of the medicine, the strength, lot number, expiry date, instructions for use and the manufacturer's address (WHO, 1997; Syhakhang, Freudenthal, Tomson & Wahlstrom, 2004). Furthermore, the WHO has extended the description of quality assurance to include all related activities and services that could affect the quality of medicines (WHO, 2004). It is thought that such a broad view of medicine quality assurance from the development stage through manufacturing, storage, distribution and dispensing would minimise the chance of patients receiving medicines with doubtful quality (Patel et al., 2009). Moreover, other quality indicators have been proposed such as patients' acceptance of their medication. This is particularly important in the case of generic medicines where patients' acceptance can offer real cost savings (Asiri & Al-Yamani, 2006). It can be concluded that medicine quality has a broad definition among different stakeholders with specific emphasis on technical specifications of medicines that can be established via laboratory testing of samples.

Medicines with poor quality could be either counterfeit or substandard (Newton et al., 2009; Newton et al., 2011). Substandard medicines or out of specification products (OOS) are defined by the WHO as products that do not meet the required specification in terms of content and ingredients (WHO, 2003a; WHO, 2012a). They are legally manufactured but do not conform to specifications as a result of inadequate manufacturing or poor storage conditions (Heyman & Williams, 2011; Yankus & Marks, 2009; Wertheimer & Norris, 2009; Clift, 2010). In contrast, the counterfeit medicines definition has a less globally accepted definition when compared to substandard medicines. The WHO definition of counterfeit medicines emphasises the act of deliberate and fraudulent mislabeling of medicines in terms of identity and/or source, indicating that counterfeit medicines could be either generic or brand (WHO, 1999a). However, other well-respected organisations, such as the U.S. Food and Drug Administration (FDA)'s definition of a counterfeit medicine, indicates that generic medicines do not fall within this scope (FDA, 2001; Alfadl, Hassali & Ibrahim, 2013).

Recently, the term Substandard/Spurious/Falsely-labeled/Falsified/Counterfeit medicines (SSFFC) was used by the WHO to describe counterfeit and substandard medicines (WHO, 2012a). This joint definition could highlight the importance of addressing both counterfeit and substandard medicines equally when medicine quality is in question.

Some researchers argue that it is necessary to distinguish between counterfeit and substandard medicines to facilitate appropriate strategies to combat each problem as it occurs (Newton et al., 2009; Newton et al., 2011). Others do not make such a distinction since both counterfeit and substandard medicines claim to be something, which in reality they are not (Amin & Kokwaro, 2007). Similarly, some view the issue of counterfeit medicines as being primarily a legal concern, while others insist that it is part of a larger medicine quality platform (Kontnik, 2006; Senior, 2008). In current times, it is important to focus the attention of the international arena on public health risks associated with substandard and counterfeit medicines rather than on debate about the terminology associated with it, in order to protect patient safety.

For the purpose of this study, the widely accepted WHO definition of counterfeit medicines was used, which defines them as "one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging" (WHO, 1999a). Similarly, the WHO definition of substandard medicines as medicines that do not conform to the required specifications (WHO, 2003a) was adopted. Both substandard and counterfeit medicines were collectively referred to as medicine quality problems or SSFFC medicines, in accordance with the WHO's most recent terminology.

1.3 Causes of medicine quality problems

The reasons for the existence of medicines with quality problems are highly dependent on the type of medicine problem, whether it is counterfeit or substandard. Typically, counterfeit medicines are associated with criminal activity and therefore are driven by high profit margins, cheap labour, mobility and low penalties for offenders, which has

attracted many to this activity in the past two decades (Ziance, 2008; Reynolds & McKee, 2010; Cheng, 2009; Shepherd, 2010; Siva, 2010). Medicines are considered attractive for illegal activity as they are easily transported, have high value per unit and are not easily distinguished from genuine samples based on visual inspection alone (Seiter, 2005). Additionally, some suggest that pharmaceutical companies, attempting to mitigate research and manufacturing costs by deploying overseas sites in weaker regulated countries, may have added additional pharmaceutical counterfeit threats (Shepherd, 2010). In contrast, substandard medicines could be a result of poor compliance to Good Manufacturing Practices (GMP), no quality demands by medicine purchasers, a declining number of quality manufacturers of essential medicines and limited awareness of healthcare professionals about the issue and the necessity to report it (Caudron et al., 2008). Other factors may also contribute to the existence of substandard medicines such as human error, limited resources and inadequate medicine regulation (WHO, 2003a). Furthermore, some suggest that low quality raw material for the active pharmaceutical ingredients (API) that are imported from developing countries such as China and India could be the reason for the existence of substandard medicines (Wilkinson, 2009).

1.4 Impact of medicine quality problems

It has been difficult to link clinical outcomes with SSFFC medicines since outcomes are routinely associated with the disease progression itself rather than suspecting SSFFC medicines (deKieffer, 2006; Liang, 2006; Newton et al., 2008; Feldschreiber, 2009; Davison, 2011). Nevertheless, it is estimated that more than 700,000 global deaths from Tuberculosis (TB) and Malaria were strongly associated with SSFFC medicines (Cockburn, Newton, Agyarko, Akunyili & White, 2005; Mackey & Liang, 2011). Other mortality incidents include contaminated heparin in the USA and sexual enhancement drugs adulterated with a large content of hypoglycemic drugs in Singapore (Kao et al, 2009; Luhn, Schiemann & Alban, 2010; Holzgrabe & Malet-Martino, 2011). Furthermore, SSFFC medicines have been related to morbidity, drug resistance, therapeutic failure and toxicity (Cockburn et al., 2005; Amin & Kokwaro, 2007; Wertheimer & Norris, 2009; Mackey & Liang, 2011; Kyriacos, Mrouch, Chahine & Khouzam, 2008). Toxicity could be a result of the presence of toxic material in some

medicines including boric acid, leaded paint, floor polish, shoe polish, talcum powder, cement powder, chalk and brick dust, nickel and arsenic (Jackson, 2009).

The economic and social impact of SSFFC medicines has also been briefly discussed in the literature. SSFFC medicines could lead to loss of productivity, inability to work and wasting limited resources, which could cause a macroeconomic burden to countries (Wertheimer & Norris, 2009). Furthermore, SSFFC medicines could decrease the profits of leading pharmaceutical manufacturers and therefore limit investment into research and drug development (Moken, 2003). Moreover, SSFFC medicines may affect society by other means: notably, loss of confidence in healthcare professionals and/or services (Cockburn et al., 2005; Amin & Kokwaro, 2007; Wertheimer & Norris, 2009; Mackey & Liang, 2011; Kyriacos et al., 2008).

1.5 Prevalence rate of substandard and counterfeit medicines

Estimating the prevalence of SSFFC medicines in a specific region or on a global scale is considered to be a difficult task. The limited amount of scientific research, variable existing definitions, limited number of reports sent to authorities, lack of resources and skills, and inadequate regulations all contribute to the complexity of the task (Amon, 2008; Newton et al., 2010; Ziance, 2008; WHO, 2010). Moreover, evidence of suspected medicines are usually destroyed, either ingested or package discarded, which complicates the estimation of the true extent of the problem even further (deKieffer, 2006; Liang, 2006). However, the WHO estimates that around 10% of all global pharmaceutical supply is SSFFC, which could reach up to 50% in developing countries and as low as 1% in the developed world (Cockburn et al., 2005; Heyman et al., 2011; Ziance, 2008). Evidence from medicine quality surveys suggests that the majority of reported SSFFC medicines were substandard rather than counterfeit, yet they receive less attention (Caudron et al., 2008; Fried, 2011). However, the United States Food and Drug Administration (US FDA) and the European Customs statistics both report a fourfold increase in investigations and seizures of counterfeit medicines in 2003 and 2006 respectively (Cockburn et al., 2005). The Pharmaceutical Security Institute (PSI), a coalition of global pharmaceutical companies to monitor and combat counterfeit medicines, reports 2,003 incidents in 2009 compared with 781 incidents in 2005 and 557 cases in 2004 (Kontnik, 2006; Davison, 2011). More recent PSI global reports

about counterfeit medicines are summarised in Figure 1.1 and the geographical location of these PSI reports is included in Figure 1.2.

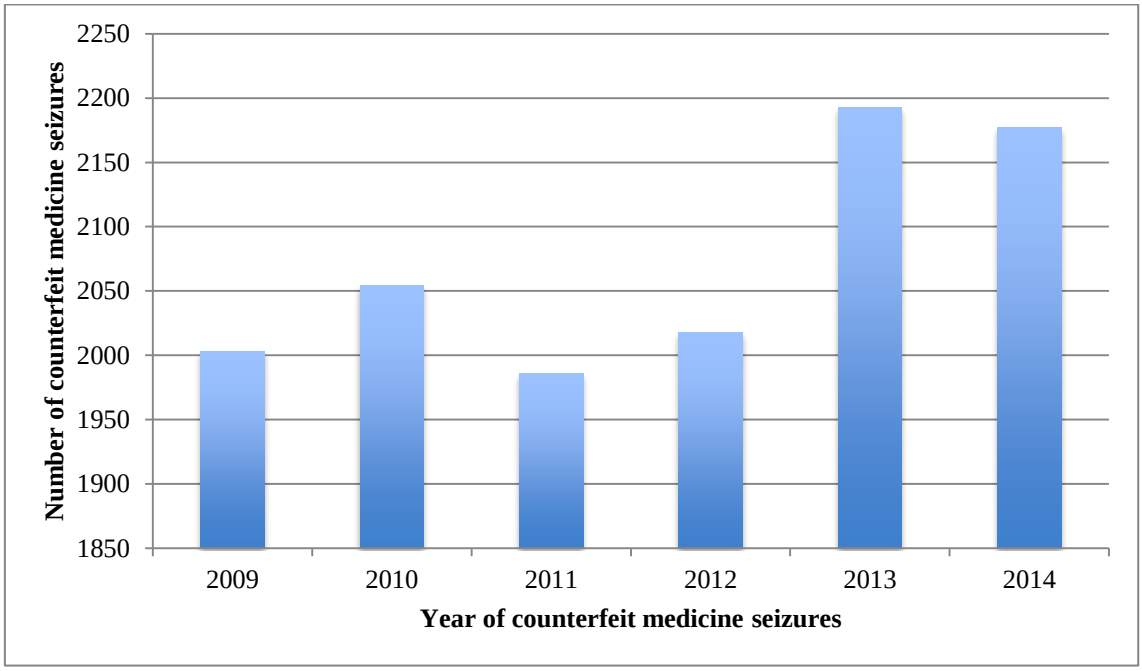


Figure 1.1 Number of counterfeit medicine seizures up to date (PSI, 2014a)

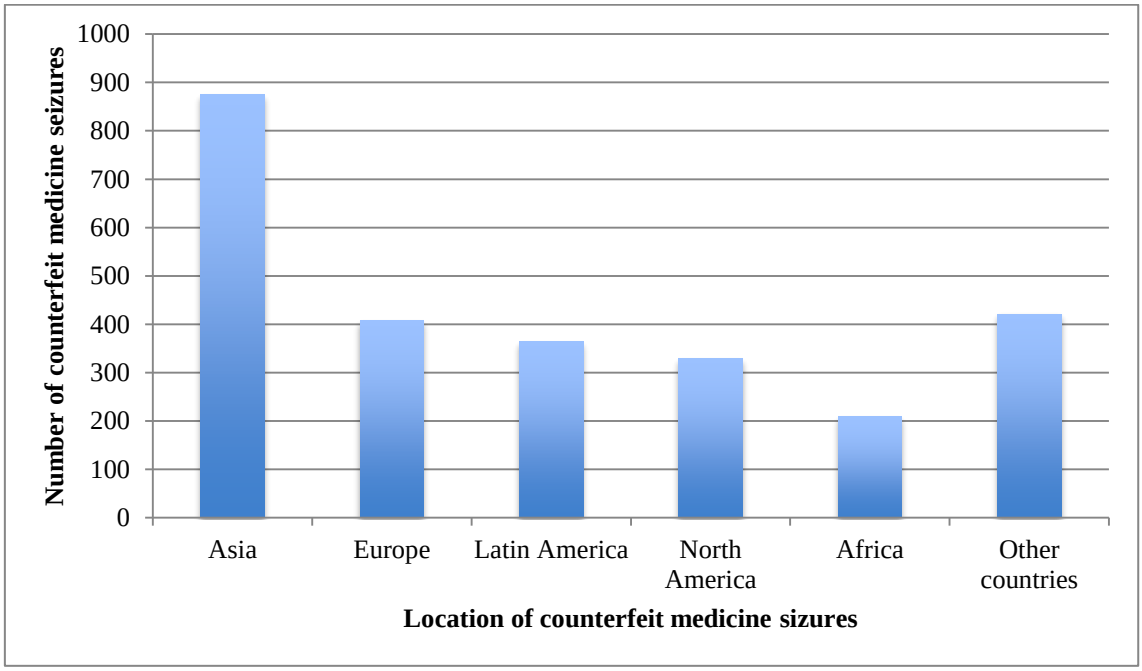


Figure 1.2 Location of counterfeit medicine seizures up to date (PSI, 2014b)

1.6 Types of substandard and counterfeit medicine problems

Several types of SSFFC medicine problems can be identified within the available medicine quality surveys in the literature. Two systematic reviews on medicine quality surveys found that the predominant types of SSFFC problems are associated with the API of the medicine itself (Almuzaini, Choonara & Sammons, 2013; Alghannam, Aslanpour, Evans & Schifano, 2014). Such problems could include unacceptable amounts of API concentration, no API or the wrong API in the medicine sample. Other less frequent types of SSFFC problems such as dissolution/disintegration failures or the presence of impurities in the medicine samples were also found within these two systematic reviews (Almuzaini et al., 2013; Alghannam et al., 2014). It is possible that these findings reflect the current predetermined objectives of such studies to focus on API rather than physical properties or medicine excipients. Further details about types of SSFFC problems in the existing literature on prospective field medicine quality surveys are found in Chapter 3.

1.7 Analysis of substandard and counterfeit medicines

The detection of SSFFC medicines is of the utmost importance to safeguard public health by a variety of different techniques. Chemical analysis techniques have been used to assess the pharmaceutical quality of samples in many medicines from different origins and settings. These analytical tools vary from well-established to fast growing emerging techniques. The combination of simple visual, chemical and physical analysis of medicines appears to be widely used in SSFFC medicine studies, and has been adopted by many developing countries for medicine screening in their markets (Lon et al., 2006; Tipke et al., 2008; Risha et al., 2008; Bate, Coticelli, Tren & Attaran, 2008). In particular, thin layer chromatography (TLC) and colorimetric tests have been widely used and described in the literature (Minzi et al., 2003; Basco, 2004, Rodomonte et al., 2010). However, these methods only confirm the presence of the API and present only semi-quantitative data, with no upper limits. Consequently, these simple, traditional methods are likely to detect unskillfully manufactured SSFFC medicines only.

Recently, the SSFCC medicine manufacturers have arguably become more sophisticated, which in turn demands equally sophisticated, analytical techniques to

detect and possibly combat their activity. Chemical analysis techniques such as Near-infrared (NIR) spectroscopy, Raman Spectroscopy and High Performance Liquid Chromatography (HPLC) are capable of detecting such sophisticated SSFFC medicines. None of the existing techniques are perfect and the study objectives, available resources and the researcher's own experience might influence the choice of method. Appendix 1 compares some of the advantages and drawbacks of a cross-section of these common analytical techniques.

1.7.1 HPLC coupled with Ultraviolet (UV) or Mass Spectrometer (MS)

High Performance Liquid Chromatography (HPLC) is a chromatographic method that has been widely used since the 1960s. The apparatus is based on a mobile phase that is pumped under pressure through a column. The column contains a stationary phase over which the analytes are carried by the mobile phase. The output of the HPLC system can be coupled with MS or UV detector (Davison, 2011; Hansen, Pedersen-Bjergaard & Rasmussen, 2012).

Several studies described the use of HPLC-UV in identification and quantification of SSFFC medicines. Shi et al. (2008) developed HPLC-UV methods to separate nine different steroidal drugs quantitatively following their identification. Sacré et al. (2011a) used impurity profiles to distinguish between counterfeit and imitation Viagra® and Cialis® using the HPLC-UV system. Further, Sacré et al. (2011b) described the development and validation of method used to detect and quantify three licensed medicines (Viagra®, Cialis® and Levitra®) and their analogues using HPLC-UV. Debrus et al. (2011) reported the development of a method that can screen nineteen different antimalarial medicines using HPLC-UV. Other studies described using HPLC-MS in SSFFC medicine analysis. Wolff, Thomson & Eckers (2003) reported the use of LC-MS in identifying the wrong API in samples of Halfan® syrup. Arthur, Wolff & Carrier (2004) found one sample that contained only lactose and lacked the stated betamethasone and dexamethasone ingredients using LC-MS. Panusa & Gagliardi (2008) developed a method for simultaneous detection and quantification of six preservatives in homeopathic syrups. Panusa, Multari, Incarnato & Gagliardi (2007) coupled HPLC with MS and UV to detect seven pharmaceuticals in counterfeit homeopathic preparations. Venhuis, Zomer, Vredenbregt & de Kaste (2010) identified

the presence of the wrong active ingredient in four counterfeit Cialis® samples using HPLC-MS following Near-Infra Red (NIR) analysis. Schad, Allanson, Mackay, Cannavan & Tettey (2008) developed a method to detect potential quality problems in isometamidium veterinary products using HPLC-MS. Further, Dorlo, Eggelte, Schoone, de Vries & Beijnen (2012) used LC-MS to confirm the absence of any miltefosine in suspected samples in Bangladesh, when blood plasma samples were collected from patients. In recent times, HPLC-MSD was successfully used to differentiate between counterfeit and genuine Cialis® tablets (Custers et al., 2016).

1.7.2 NIR spectroscopy

NIR was not a popular analytical method until the 1960s, when Karl Norris recognised its potential in analysis for a variety of industries (Hart, Norris & Golumbic, 1962; Jamrógiewicz, 2012). In the 1970s, NIR started to be used extensively in several industries around the world. At the end of 1990s, NIR gained the pharmaceutical industry's acceptance and has been included in the European Pharmacopeia since 1997 (Rodionova & Pomerantsev, 2010). The NIR instrument mainly consists of a laser and a detector. The infrared spectrum is divided into 3 sub-regions: near, mid and far, according to proximity from the visible region (Davison, 2011). The NIR region covers the wavelengths between 700 nm to 2,500 nm (Scafi & Pasquine, 2001; Cui, Zhang, Ren, Liu & Harrington Pde, 2004). In this region, it is possible to observe C-H, N-H and O-H bonds present in organic molecules, represented by overtones and the combination of absorption bands in the mid-IR region (Scafi & Pasquine, 2001; Cui et al., 2004; Rodionova & Pomerantsev, 2010). The light from the laser would interact with a given sample and would be absorbed at specific frequencies, according to the molecular properties of the sample itself. Thus, forming a chemical fingerprint of the sample, which can be cross-referenced with spectra databases and can thus generate useful information (Davison, 2011). This generated chemical fingerprint or spectra is characteristic of each pharmaceutical formulation and, therefore, samples from different manufacturers may give rise to different spectra (Scafi & Pasquine, 2001). NIR is useful in identification and/or quantification of an active pharmaceutical ingredient and excipient, and in determining physical attributes of a drug such as particle size, crystalline form, polymorphism, hardness, dissolution behaviour, disintegration pattern (Hansen et al., 2012; Jamrógiewicz, 2012). In short, NIR application can be useful

throughout the lifetime of a medicine from the manufacturing process up to the post-marketing surveillance step of the final product.

NIR has been used in the literature for the detection of SSFFC medicines in some international markets. Storme-Paris et al. (2010) tested the discriminating powers of NIR using various samples of fluoxetine and ciprofloxacin in France. Said, Gibbons, Moffat & Zloh (2010) compared NIR spectra of different paracetamol batches obtained from Malaysia and UK. Polli, Hoag & Flank (2009) tested eight suspected samples purchased from Hong Kong using handheld NIR. Fernandes, da Costa, Valderrama, Marco & de Lima (2012) used NIR to differentiate brand and generic glibenclamide tablets in Brazil. The Chinese experience with handheld NIR for detection of counterfeit medicines and tracking movement of drugs in the supply chain should also be highlighted (Feng, Yang, Yang & Hu, 2011). It can be concluded that NIR is a powerful analytical tool for identification and quantification of medicines, and provides both chemical and physical information for better assessment of samples. However, it is mostly used as a screening tool, as it cannot identify unknown samples, so other complementary techniques are needed for identification such as HPLC, Nuclear Magnetic Resonance (NMR) or Liquid Chromatography-Mass Spectrometry (Vredenbregt, Blok-Tip, Hoogerbrugge, Barends & de Kaste, 2006).

1.7.3 Raman spectroscopy

Raman Spectroscopy is based on light scattering phenomena, unlike NIR that is based on absorption. When light from a high-powered laser beam interacts with a sample, most of the light retains the same frequency, except around one in a million of the scattered photons that change frequency, to create what is called a Raman effect (Davison, 2011; Martino, Malet-Martino, Gilard & Balayssac, 2010). In recent years, Raman techniques have been increasingly utilised to screen for medicine quality problems. De Veij, Deneckere, Vandenabeele, de Kaste & Moens (2008) used Raman for the detection of 18 different Viagra® tablets, which were all found to contain the correct API but with different excipients. Furthermore, de Peinder, Vredenbregt & de Kaste (2008) successfully used Raman in discriminating between authentic and counterfeit Lipitor® obtained from different sources. It has also been shown that Raman techniques were able to detect early chemical changes caused by inappropriate storage

conditions for acetylsalicylic acid tablets (Neuberger & Neusüß, 2015).

1.7.4 Visual, physical and authentication of source of medicine samples

Chemical testing is not the only type of analysis that can be performed on suspected SSFFC medicine samples. Physical analysis can be performed to complement chemical analysis particularly disintegration and dissolution tests for solid dosage forms. This can be attributed to the availability of specific physical tests in different pharmacopoeias in addition to the use of physical information about the medicinal product to predict the bioavailability of medicines (Rookkapan et al., 2005; Amin, Snow & Kokwaro, 2005; Gaudiano et al., 2007). However, this could only be used as an indicator and cannot substitute bioavailability studies that can be lengthy and expensive (Kenyon et al., 1999; Kayumba et al., 2004).

Package inspection is another type of medicine analysis, which can be found in medicine quality surveys in the literature. Problems with medicine packaging could include signs of obvious spelling errors, suspicious holograms when compared with known genuine samples, peculiar medicine taste and/or odour and also basic label information such as the medicine name, dosage, manufacturer details, expiry date and lot number. The WHO definition of counterfeit medicines (WHO, 1999a) signifies packaging information as a source of information to detect counterfeit medicines. The World Health Professions Alliance (WHPA) and The International Pharmaceutical Federation (FIP) had developed a tool for visual inspection of medicines that can be utilised for a systematic package inspection in medicine quality surveys (FIP, 2013).

The authentication of medicine source through contact with manufacturers or authorities is another mode of inspection for medicine quality that could be less popular than the previously mentioned methods. Limited communication and feedback towards such queries could be a reason for its limited use (Khan et al., 2010; Nair, Strauch, Lauwo, Jahnke & Dressman, 2011). It could also be possible that the scope of a study did not consider the possibility of counterfeiting and focused only on substandard medicine issues.

1.8 Perception about medicine quality and related problems

The research on medicine quality has been largely focused on laboratory testing of the actual medicine quality worldwide (Patel, Gauld, Norris & Rades, 2010). Few researches have investigated the perceptions about medicine quality and related problems from the perspective of different stakeholders. This could be a reflection of the complexity of such projects as different points are at stake. Failure of treatment because of wrong diagnosis, inappropriate medicine or dosage selection, patients' non-adherence, medication errors or adverse drug reactions, could be easily confused with poor quality medicines (Quick et al., 1997). Further, medicines can be regarded as different from other products since their quality cannot be determined visually in the absence of sophisticated laboratory methods for the confirmation of quality results (Quick et al. 1997; Patel et al., 2010).

Of the limited available research articles investigating medicine quality without the laboratory testing of medicine samples, some have used a general approach about medicine quality from the perspective of medicine sellers, manufacturers, distributors, consumers and healthcare providers in Laos and South Africa respectively (Syhakhang, Freudenthal, Tomson & Wahlstrom, 2004; Patel et al., 2009; Patel et al., 2010; Patel, Gauld, Norris & Rades, 2012). The majority, however, investigated counterfeit medicines specifically in terms of risk, convenience of obtaining such products, knowledge, barriers, perception, practices, attitudes, related factors, difference in opinion between healthcare providers and patients, in addition to reviewing court sentences on offenders (Sugita & Miyakawa, 2010; Law & Youmans, 2011; Khan et al., 2011; Alfadl et al., 2012; Shahverdi et al., 2012; Alfadl et al., 2013; Binkowska-Bury et al., 2012a; Lai & Chan, 2013). Other studies have focused on measuring responses of the public towards local and governmental campaigns against counterfeit medicines in Africa (Abdoulaye, Chastanier, Azondekon, Dansou & Bruneton, 2006; Cuchet-Chosseler, Bocoum, Camara, Abad & Yamani, 2011; Oladepo, Brieger, Adeoye, Lawal & Peters, 2011). The majority of these studies have been conducted in developing countries and only some in developed areas of the globe such as Japan (Sugita & Miyakawa, 2010) and the USA (Law & Youmans, 2011).

There were some interesting findings from these studies and other related investigations examining the issue of medicine quality without laboratory analysis of samples. Counterfeit and substandard medicines have been shown to be confused with other issues such as generic medicines by some patients (Sarradon-Eck, Blanc & Faure, 2007; Håkonsen & Toverud, 2011). Some evidence in developing countries suggests that patients and healthcare providers are dubious about healthcare services and medicines that are available free of charge and consider them to be of inferior quality (Lo¨nnroth, Tran, Thuong, Quy & Diwan, 2001; Patel et al., 2010). Medicine quality has been previously described in terms of effect on felt symptoms by healthcare providers and patients in Laos and South Africa (Syhakhang et al., 2004; Patel et al., 2010; Patel et al., 2012). Executive medicine wholesalers have described medicine quality in terms of the product itself and the process involved in the manufacturing and handling of the medicine (Patel et al., 2009). Counterfeit medicines were defined as a product without local registration in Cambodia by wholesale managers (Khan et al., 2011). In Poland, lay people have shown a higher level of knowledge about the scale of counterfeit medicines and the associated threats when compared to local physicians and nurses (Binkowska-Bury et al., 2012a). Pharmacists in Iran have shown high awareness of counterfeit medicines but low levels of knowledge and practices related to the subject (Shahverdi et al., 2012). Moreover, a clear difference between low perception about medicine quality and the actual good medicine quality following laboratory analysis has been reported in South Africa (Patel et al., 2012).

1.9 Generic medicines

A generic medicine is defined by the WHO as "a pharmaceutical product, usually intended to be interchangeable with an innovator product that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights" (WHO, 2015). The generic medicine should be identical to the innovator product in terms of use, quality, safety, efficacy, dosage form, strength and route of administration (FDA, 2015a; EGA, 2015). However, generics can differ from the innovator product in terms of inactive ingredients, shape, colour and packaging (FDA, 2015a; FDA, 2015b; EGA, 2015). Generic medicines should also demonstrate bioequivalence to the innovator product in order to obtain market authorisation from different regulatory systems (Davit, Braddy, Conner & Yu, 2013). The bioequivalence

tests ensure that no significant differences are present between an innovator and a generic medicine in rate and extent of absorption (King & Kanavos, 2002; Hassali et al., 2014). Occasionally, the bioequivalence study requirement may be waived if a given product demonstrates high solubility and high permeability for example (FDA, 2015b; Hassali et al., 2014).

Generic substitution and generic prescribing are strategies adopted by many healthcare regulators in the world to promote generic medicines (Vogler, 2012). The possible explanation is that generic medicines offer a substantial reduction in the cost of medicine in a healthcare industry where medicines are considered the second largest source of expenditure, second only to healthcare workers' wages (Matin, 1999; Shafie & Hassali, 2008; Marchildon & DiMatteo, 2011). The generic substitution can be described as the act of substituting a prescribed brand medicine with an equivalent generic when dispensed and the generic prescribing is the act of prescribing the medicine by its International Non-Proprietary Name (INN) of the medicine (Ferner, Lenney & Marriott, 2010). It has been suggested that generic substation should not be considered a simple task but rather a complex task that involves many considerations such as the patient preference, patient consent, prescriber's approval, patient's understanding of the difference between the medicine brands to prevent any confusion, the assessment of allergy history to any inactive ingredients and the healthcare professional's own judgment for patient suitability for generic substitution (Duerden & Hughes, 2010; Alrasheedy, Hassali, Aljadhey, Ibrahim & Al-Tamimi, 2013). Furthermore, it is important to recognise that not all medicines may be suitable for generic substitution. For example, Narrow Therapeutic Index (NTI) medicines, modified release preparations of medicines, medicines containing more than one active ingredient and products using different salts to form the active ingredients could not be interchanged routinely (Ferner et al., 2010; Duerden & Hughes, 2010; Lewek & Kardas, 2010).

The perception about generic medicines has been explored in some studies. Some patients believe that generic medicines have inferior quality, safety or effectiveness when compared with brand medicines (Sansgiry, Bhosle & Pope, 2005; Shrank, Cox,

Fischer, Mehta & Choudhry, 2009; Albadr & Khan, 2014; Kjoenniksen, Lindbaek & Granas, 2006; Babar et al., 2010; Albarraq, 2013). However, other studies have reported that some patients do not believe that generic medicines have any safety risks (Heikkilä, Mäntyselkä & Ahonen, 2010). Negative views about generic medicines have also been associated in the literature with some healthcare professionals. There were some physicians that expressed such opinions regardless of whether the medical regulatory authorities were strict in their countries (Hassali et al., 2014). Several reasons were suggested to contribute to such negative perception about generics medicines from different stakeholders. Lack of awareness about generic medicine registration and bioequivalence testing could be a factor from the healthcare professionals' view (Shrank et al., 2011; Chua, Hassali, Shafie & Awaisu, 2010).

1.10 Saudi Arabia

1.10.1 Country profile

Saudi Arabia is one of the largest countries in the Middle East with a population of around 27 million people according to the 2010 National Census and this has been expected to rise up to 29 million in 2012. According to the latest population estimation, The Central Department of Statistics and Information (CDSI) in Saudi Arabia predicts that 19 million of the whole population are Saudi nationals while the remaining 10 million are expatriates (CDSI, 2013).

Geographically, the country can be divided into five distinctive regions: Central, Western, Eastern, Southern and Northern region. Both Central and Western region account for approximately two thirds (64%) of the whole population, which is evenly divided between them. The Eastern and Southern regions accommodate 15% of the whole population within each. The remaining 6% of the population occupy the Northern region (CDSI, 2013).

Administratively, the country is divided into thirteen different provinces, each with its own governor. The majority of the population (65%) resides in three provinces: Riyadh (25%), Mecca (25%) and The Eastern province (15%). The remaining 35% of the population are distributed among the remaining ten provinces. Four cities (Riyadh, Jeddah, Mecca and Medina) have a population of more than one million in each city.

Another four cities (Dammam, Hafouf, Taif and Tabouk) have a population of more than 500,000 people. Furthermore, there are nineteen other cities with a population of more than 100,000 in each city (CDSI, 2013). Appendix 2 illustrates the population figures of provinces and cities according to their geographical locations, based on the latest 2010 national census in the country.

1.10.2 Chronic disease in Saudi Arabia

Diabetes Mellitus is one of the most common chronic diseases in Saudi Arabia, with an estimated prevalence rate of 24% among the adult population, and is considered one of the highest figures worldwide (Salman & Al-Rubeaan, 2009; Eledrisi et al., 2007). Chronic diseases are among the leading mortality causes worldwide and are responsible for 71% of reported deaths in Saudi Arabia according to the WHO. Cardiovascular diseases, cancer and diabetes are responsible for 42%, 9% and 6% respectively for all mortality rates reported in the country. The WHO estimates a high percentage of risk factors present in the adult Saudi Arabian population, such as high blood pressure (33%), high blood sugar (18%), obesity (33%), smoking tobacco (24%) and high cholesterol levels (36%), which could further add to possible comorbidities associated with these chronic diseases (WHO, 2013a). Interestingly, high blood sugar and obesity are the only metabolic risk factors that have been constantly rising in Saudi Arabia since 1980 according to the WHO data and therefore could require particular attention.

Glycemic control has been shown to improve health outcomes of diabetic patients and prevent serious long-term complications (Salman & Al-Rubeaan, 2009; Eledrisi et al., 2007). However, in a cross-sectional study set in Saudi Arabia, a significant 28.5% of diabetic patients were presented with poor glycemic control (Eledrisi et al., 2007). It is therefore essential to maintain acceptable glycemic levels among diabetic patients by all possible means, which could also include prevention of medicine quality problems.

1.10.3 Healthcare system in Saudi Arabia

Healthcare services started in Saudi Arabia with the establishment of a public health department in Mecca in 1925 to serve both the population and pilgrims. The establishment of the Ministry of Health (MOH) in 1950 followed to extend healthcare services in the country. In 1970, a governmental five-year plan was proposed to

improve all public sectors including healthcare services (Almalki, Fitzgerald and Clark, 2011).

The Saudi healthcare system is currently undergoing continuous improvements accompanied by annual increases of the budget allocated to the MOH by the government of Saudi Arabia (MOH, 2011; Alsultan et al., 2012; Bawazir, 2004).

The MOH is the primary governmental healthcare provider in the country. It currently operates 251/420 (60%) of all hospitals in the country. Further, it established 2,109 primary health care clinics distributed throughout Saudi Arabia (Almalki et al., 2011; MOH, 2011). However, the MOH is not the only government healthcare provider in Saudi Arabia, as other Ministries such as the Ministry of Defense, Ministry of Interior and the Ministry of National Guard offer healthcare services to their employees and their dependents at a primary, secondary and tertiary care level, and may refer clinical cases between them according to their area of expertise (Asiri & Al-Arifi, 2011; Al-Shammari, Jarallah & Felimban, 1997; MOH, 2011). Additionally, it is estimated that 70% of all hospital visits by patients were to government healthcare providers, predominantly influenced by free of charge health care services including prescription medicines (MOH, 2011; Abou-Auda, 2002; AbuYassin et al., 2011; Bawazir, 2004). An overview of the healthcare system structure in Saudi Arabia can be found in Figure 1.3.

Private healthcare is also provided in Saudi Arabia through private hospitals, polyclinics and private clinics. However, unlike governmental healthcare facilities, fees must be paid for using private healthcare services including prescription medicines. The fees paid can either be directly by the patients or via medical insurance provided by some employers, or in certain circumstances patients may want to purchase health insurance for themselves. Currently, there are 130 private hospitals, 2,185 polyclinics and 198 private clinics operating in the country (MOH, 2011). Interestingly, more than 50% of all private healthcare facilities in the country are located in the cities of Riyadh and Jeddah alone.

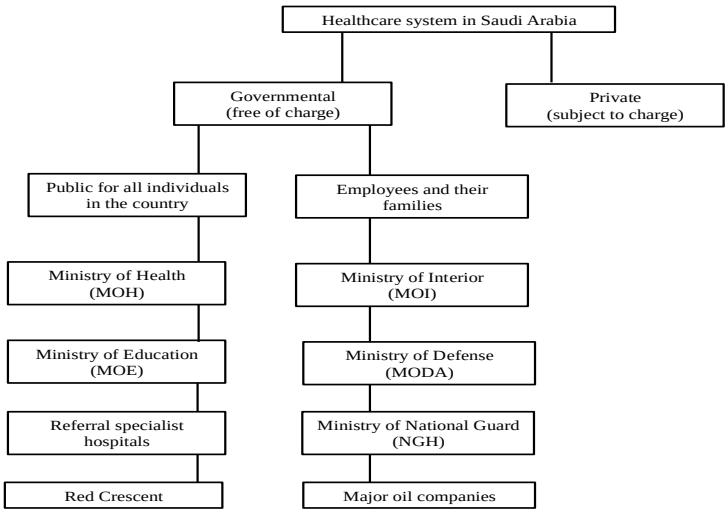


Figure 1.3 Overview of the healthcare system structure in Saudi Arabia

1.10.4 MOI-MSD

The Ministry of Interior Medical Supply Department (MOI-MSD) is one of the major governmental healthcare providers to their staff and families in Saudi Arabia (MOIMSD, 2015). It currently operates three secondary care hospitals in Riyadh, Dammam and Makkah. The hospital in Riyadh has an inpatient capacity of more than 500 beds and had been in service for more than forty years. The hospitals in Makkah and Dammam have between 100 and 200 beds respectively as they have both been recently established less than four years ago.

However, the majority of annual patient visits in the MOI-MSD, estimated to be around two million visits each year, are focused on the primary care clinics. The MOI-MSD operates 18 regional primary clinics located in different cities in the country in addition to 3 major primary clinics in the capital city of Riyadh. The majority of these primary clinics have been established for more than 20 years with some exceptions such as the primary clinics in Bisha and Alkharj. Furthermore, all of these previously mentioned primary clinics have clinics for the major types of medical care including cardiovascular, gastrointestinal, obstetric gynecology, respiratory, dermatology and

neurological clinics.

According to the latest available MOI-MSD statistical report (currently in publication), there are 293 physicians and 71 pharmacists working in the MOI-MSD primary clinics. In addition, there are more than 400 other members of staff in the MOI-MSD primary clinics including laboratory technicians, x-ray technicians, nurses and other administrative staff.

1.10.5 Medicine supply chain in Saudi Arabia

In recent times the pharmaceutical industry in Saudi Arabia has significantly changed with the establishment of The Saudi Food and Drug Authority (SFDA) in 2003 and The National Unified Procurement Company for Medical Supplies (NUPCO) in 2010 (SFDA, 2015a; NUPCO, 2015). Although both organisations may require some time to achieve their full potential, they are predicted to be major stakeholders in the near future. The SFDA is now the independent body responsible for regulating, pricing, ensuring safety, security, efficacy and analysis of all imported and locally produced food, medical devices and medicines in Saudi Arabia. SFDA employees are working in collaboration with Customs Clearance at all major Saudi ports to track and clear imported food and drug supplies (SFDA, 2015a). Conversely, NUPCO is the government-funded logistics company which will be responsible for all medical and pharmaceutical logistic operations in the country, once fully operational. The logistic operation of NUPCO will include procurement, warehousing and distribution of all pharmaceutical and medical equipment on behalf of all government healthcare providers in Saudi Arabia.

Medicines in governmental healthcare providers are now mainly procured through a tendering system in order to lower medication costs. Tender systems can be through a group tendering system such as the Group Purchasing Program for the Gulf Countries (GPP) and/or local tenders in each governmental institute. The Gulf Countries GPP includes pharmaceutical and medical equipment annual tenders, in which governmental institutes from all seven Gulf countries (Saudi Arabia, United Arab Emirates (UAE), Kuwait, Qatar, Oman, Bahrain and Yemen) are eligible to participate (SGH, 2014). Saudi Arabia participates in this Gulf GPP with representatives from all government

agencies which provide healthcare services as described earlier. Therefore, medicines procured from the Gulf GPP by all governmental institution in Saudi Arabia and neighboring Gulf countries are mostly similar, which highlights the impact of medicine quality studies on a large population. Figure 1.4 briefly describes the Gulf Countries GPP annual tender cycle for medicine procurement.

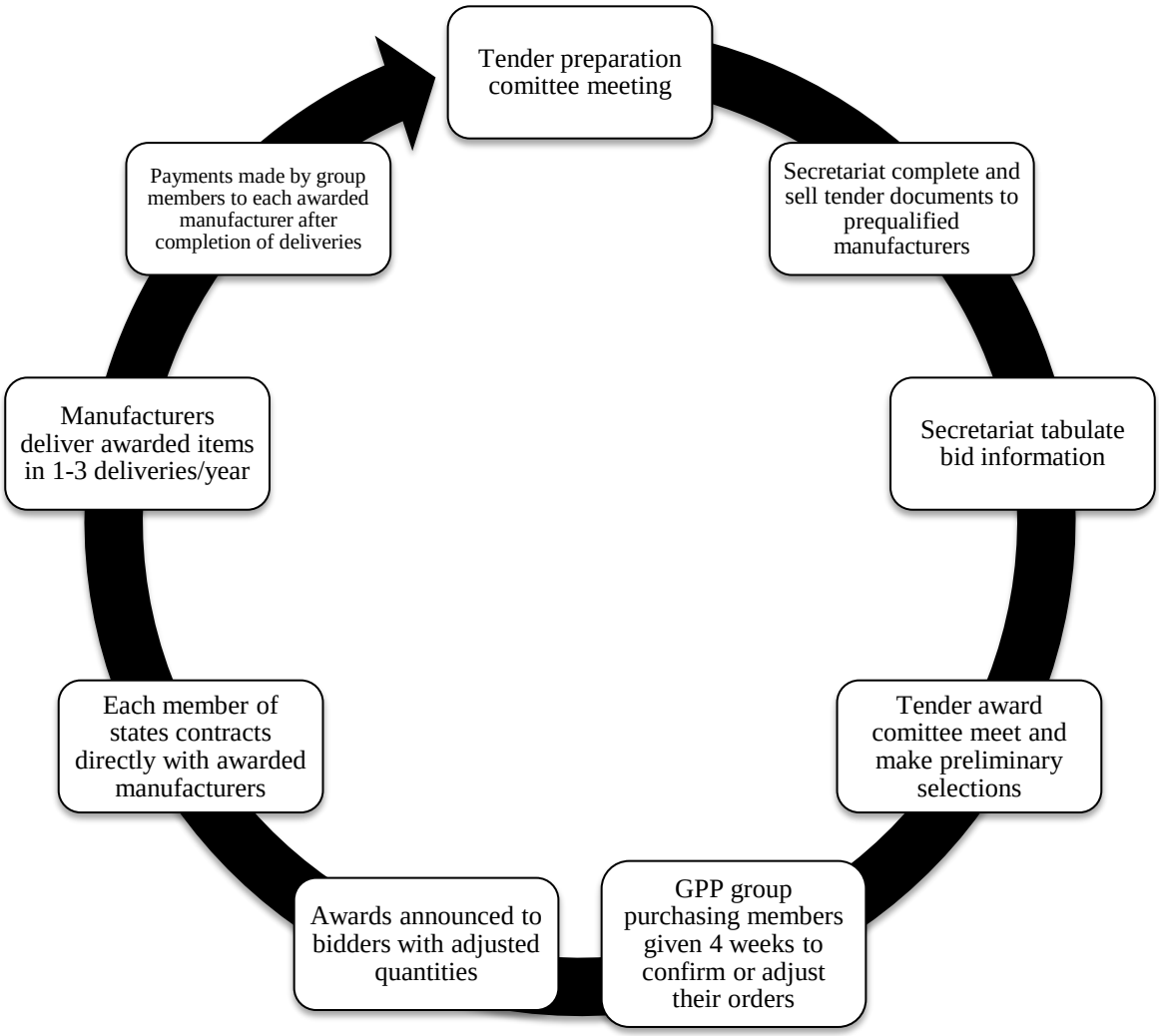


Figure 1.4 Annual GPP tender cycle (DeRoeck et al., 2006; SGH, 2014)

In contrast, government healthcare providers may require direct procurement from medicine suppliers in certain circumstances, particularly when medicines are urgently needed. Typically, the required items are sent in the form of quotation requests to a list of manufacturers and/or wholesalers. The vendors will then prepare quotations to be sent either by fax or directly to the procurement department in a given institution. Consequently, one quotation will be accepted and a single manufacturer will be awarded a purchase order to deliver the items within the specified time limits to avoid financial penalties. However, direct purchase of medicines is strongly regulated and discouraged, and can only be acceptable in the event of emergencies, unavailability of a required medication in the medicine formulary or in the absence of tender quantities of a specific medication. Furthermore, in rare cases a required medicine may not be available through a tender system, which eliminates the options available to the procurement department in any governmental organisation and using the direct purchase scheme becomes inevitable. In such cases, the responsibility of the SFDA remains in allowing these medicines to enter the country by providing portal clearance letters and ensuring the quality of these medicines through appropriate documentation and/or laboratory analysis.

The medicine supply chain in the Saudi Arabian private sector is somewhat different than the governmental sector. Major private hospitals could procure their medicines via a tender system, but are not obligated to choose this route of procurement in contrast to public healthcare organisations in Saudi Arabia. Similarly, community pharmacies routinely procure medicines directly from the manufacturers in the country as their required medicine quantities and available staff may not support a decision to procure medicines via a tender system. The responsibility of the SFDA remains in this case to ensure the quality of medicines available in these settings and their adherence to the available pharmaceutical laws that govern the appropriate location of pharmacies; staff authorised to dispense medicines and types of medicines available for sale for example.

1.10.6 Substandard and counterfeit medicine in Saudi Arabia

In Saudi Arabia, official reports on SSFFC medicines are limited. The predominant source of information appears to be newspaper articles, similar to many countries

(Cockburn et al., 2005). However, the country is thought to have a lucrative market for all counterfeit materials, having an estimated 4 billion US dollar market of counterfeits and piracy trade (Havocscope, 2011).

The SFDA has issued some warnings regarding counterfeit medical products and pharmaceuticals in the past. In 2011, a warning about one batch of the oral antibiotic Augmentin 1g was released, which was found to contain the wrong active ingredient following analysis in the SFDA laboratories (SFDA, 2011a). Moreover, warnings about counterfeit medical products such as aerosol chamber devices and counterfeit herbal and cosmetic agents were also issued (SFDA, 2011b; SFDA, 2011c). However, no recent information was available in the SFDA public domain regarding counterfeit medicine seizures in Saudi Arabia.

Pharmaceutical companies in Saudi Arabia estimate that 30-40% of circulating medicines in pharmacies and hospitals in the country are counterfeit (Saudi Gazette, 2008). In contrast, the SFDA insists that only 0.5% of medicines in the country are counterfeit (Arabnews, 2010). Additionally, there has been no reported prevalence of the level of substandard medicines in the country. The recent growing public concern about substandard and counterfeit medicines might have triggered the local councils to recommend amendments in the country's pharmaceutical laws, to increase sentences and penalties for offenders (Arabnews, 2011).

A limited number of research articles investigated SSFFC medicines in Saudi Arabia. Kyriacos et al., (2008) analysed four Amoxicillin samples from Saudi Arabia and found that 2/4 (50%) of samples did not meet USP API% limits. Afifi & Ahmadeen (2012) evaluated several Metformin brands marketed in the country and all were found to contain acceptable API% according to USP. Other studies found failure of disintegration among marketed vitamins in Saudi Arabia (Maswadeh & Al-Jarbou, 2011). A recent study found that amoxicillin samples sold in nine community pharmacies in Riyadh did not contain the acceptable pharmacopoeial quantities of the active pharmaceutical ingredient (Khoja et al., 2013a).

1.11 Scope and focus of thesis

A literature review on the subject of counterfeit and substandard medicines has shown that a systematic detail of prospective medicine quality studies was not available. The major focus of the current literature, particularly in the developed world, was on the development of laboratory based and field detection methods for counterfeit medicines. There were fewer published research studies focusing on substandard and counterfeit medicine prevalence rates, particularly in some areas of the developing world, such as the Middle East. Furthermore, the issue of perception about medicine quality and related problems was rarely addressed in the literature worldwide. No study has been identified to address these issues simultaneously in Saudi Arabia. The findings of this study would support decision makers and the interested population in increasing the understanding about the issue of substandard and counterfeit medicines from a laboratory-based perspective and the stakeholders' perspective. This approach would be beneficial in gaining a comprehensive understanding about laboratory-based facts versus the perceptions of different stakeholders with regard to medicine quality and their problems. Such an approach could be invaluable for making investment decisions towards laboratory analysis or towards public health campaigns, particularly in limited resource settings. Furthermore, this study could be used as a template for future studies regarding the issue of medicine quality and related problems in different countries and healthcare settings.

This thesis will generally focus on medicine quality and SSFFC problems in the MOI-MSD healthcare settings in Saudi Arabia from a laboratory and stakeholders' perspective. The thesis will include two systematic reviews (Chapters 3 and 5) of the relevant literature, laboratory analysis of glibenclamide (Chapter 4), a qualitative study investigating the stakeholders' perceptions of the related issues (Chapters 6 and 7) and a final discussion regarding the research study. More specifically, the first systematic review (Chapter 3) assisted in identifying common SFFCC problems; the precise type of analysis performed; and to identify knowledge gaps to consider in the later parts of the study. The analytical part (Chapter 4) has focused on the chemical analysis of one selected diabetes medicine (glibenclamide) in terms of API quantities within the acceptable USP pharmacopoeial limits using HPLC, in addition to authentication of

source and visual analysis. A second systematic review (Chapter 5) assisted in identifying the existing literature about knowledge and perceptions of stakeholders regarding medicine quality and their problems. The qualitative side of the study (Chapters 6 and 7) included in-depth exploration of various MOI-MSD stakeholders including commissioners', patients', pharmacists' and physicians' perceptions about medicine quality and its related problems. This thesis has not examined glibenclamide samples by physical analysis; examined other medicine constituents such as excipients or attempted to develop novel methods for SSFFC laboratory analysis, as it was not part of the study objectives. Furthermore, the findings of the qualitative part and the analytical part of the study are limited by the location and time of the data collection period, from August 2013 till December 2014.

1.12 Aim of the study and research questions

The overall aim of this study is to explore medicine quality and perception among the stakeholders in the MOI-MSD clinical settings in Saudi Arabia using glibenclamide as an indicator. The main objectives of this study include:

1) Using glibenclamide as an indicator, to establish whether the randomly selected samples meet the quality control criteria of API quantity through chemical tests, visual tests and verification of source where possible.
2) Describe the nature of any glibenclamide failed samples, if found.
3) Establish commissioner, patient and healthcare providers' beliefs about the quality of medicines available at MOI-MSD in Saudi Arabia and any related problems.
4) Explore the knowledge and behaviour of MOI-MSD commissioners, healthcare providers and patients about medicine quality and related problems.

The research questions that will be addressed in this thesis are as follows:

1) Are there any SSFFC medicines in the glibenclamide samples collected from MOI-MSD healthcare services in Saudi Arabia in terms API quantity, appearance and source?
2) What are the characteristics and nature of SSFFC glibenclamide samples in MOI-MSD in Saudi Arabia if found?

3) What are the perceptions of commissioners, healthcare providers and patients in MOI-MSD about the medicine quality and related problems?
4) What is the knowledge about medicine quality and behaviour associated with doubtful quality medicines among commissioners, healthcare providers and patients in MOI-MSD healthcare services?

2 Chapter 2: Research context and methodology

This chapter will contain information about the research context and methodologies used in this study. It will explain the theoretical framework and justify the use of methods. Furthermore, it will describe the research design and methods used in order to answer the research questions and fulfill the research objectives.

2.1 Theoretical framework

The theoretical framework provides a set of justifications for the research on different levels. It justifies the philosophical assumptions of the researchers themselves through the views they hold on epistemology and ontology (Creswell, Plano Clark, Gutmann & Hanson, 2003; Bryman, 2012), theoretical paradigms/perspectives held and choice of methodology/methods in the study (Crotty, 1998). On a practical level, the theoretical framework would influence and justify the study design, settings, sampling, data analysis and interpretation (Gerhard, 2008).

2.1.1 Epistemology and ontology

Epistemology entails the nature of knowledge, possibility, scope and basis (Hamlyn, 1995). It can be associated with what is considered appropriate knowledge about the social world (Bryman, 2012). Therefore, it gives a philosophical ground to the type of knowledge possible and how we can ensure its adequacy (Maynard, 1994). Epistemological positions could include objectivism (presumes all knowledge is out there and humans only need to discover it), constructivism (rejects objectivism and considers knowledge to be a product of social engagements between subject and object) and subjectivism (meaning is imposed on the object by the subject) according to some researchers (Crotty, 1998). Ontology is concerned with whether the social world is regarded as something external to social factors or something that people are perceiving or constructing now (Bryman, 2012). Therefore, ontological positions could be either objectivism (social phenomena and their meaning have an independent existence from social factors) or constructivism (social phenomena and their meaning continue to be constructed by social factors) according to some researchers (Bryman, 2012). Within the context of this study, objectivism was adopted in the analytical part of the study and constructivism was adopted in the qualitative part of the study.

2.1.2 Theoretical paradigms

Theoretical paradigms or perspectives entail a philosophical stance to inform methodology and provide context for process, explains its logic and criteria (Crotty, 1998). Others have described it as a set of clusters and beliefs about what should be studied, how it should be studied and how results should be interpreted (Kuhn, 1996; Bryman, 1988; Bryman, 2012). In a sense, theoretical paradigms or perspectives can describe the ways in which we look at the world. Often, they are not addressed by the researchers and remain largely hidden in the research context (Slife & Williams, 1995). Four common types of world views exist and will be further discussed namely positivist, constructivist, emancipatory and pragmatist. In healthcare research including pharmacy practice, two paradigms often come into conflict namely the biomedical and social model (Jesson & Pocock, 2001).

The biomedical model can be regarded as the principle model in healthcare research. The theoretical framework that follows this model is called positivism which emphasises objective and numeric measures to generate knowledge by establishing cause and effect relationships. Research in pharmacy has long been based on a positivist philosophical approach to science and the world, while limited attention has been given to the social world which would require a social science approach (Jesson & Pocock, 2001; Creswell, 2009). In contrast, the social model emphasises the social action where some believe that not all diseases or phenomena can be detected by biochemical means, particularly where subjective feelings and perceptions of a disease or phenomena is present in a theoretical framework that can be described as constructivist. Social science often uses different methods to explore a single phenomenon in a similar approach to their paradigm (Jesson & Pocock, 2001; Creswell, 2009). Furthermore, emancipatory or advocacy/participatory paradigm is another school of thought that demands change through creation of political debates and actions (Creswell, 2009). On the other hand, pragmatism focuses on the problem itself rather than the philosophical background in order to liberate the researcher to use a single or multiple approach(es) in order to investigate phenomena based on what works at that point in time, which may be best suited with a mixed method approach as a research strategy of inquiry (Creswell, 2009).

The framework of this research was formulated based on consideration of how to answer the research questions and meet research objectives in a suitable manner. In one phase of the study, glibenclamide samples were the subject of enquiry for possible quality problems mainly in laboratory settings to establish facts about medicine quality. In another phase of the study, the perceptions of stakeholders in MOI-MSD in Saudi Arabia about medicine quality and its related problems were the subject of inquiry in order to clearly establish their beliefs and views regarding this phenomena. Therefore, in order to answer the research questions and meet the research objectives of the study, a pragmatic paradigm using a mixed-method approach as a strategy of enquiry was adopted in order to facilitate answering the variety of research questions in this study. Within this context, a quantitative study was used to identify any common medicine quality problems associated with the API quantity in the laboratory, authentication of source and packaging information in glibenclamide samples collected from the MOI-MSD in Saudi Arabia. On the other hand, a qualitative study was used to explore the perceptions of MOI-MSD stakeholders (i.e. commissioners, physicians, pharmacists and patients) about medicine quality and related problems such as counterfeit medicines through a focus group discussion, semi-structured interviews and self-completed survey questionnaires.

2.1.3 Mixed method approach

Mixed methods research is a type of research strategy that is often referred to as a third paradigm of research enquiry (Johnson & Onwuebuzie, 2004; Abdul Hadi, Alldred, Closs & Briggs, 2013). This strategy is arguably the most emerging research strategy and is closely related to the pragmatism paradigm of worldview (Creswell, 2009). Although mixed methods research has been increasingly used by researchers, its adaptation in pharmacy practice research remains limited possibly because of lack of clear understanding of what it is and the benefits of its use (Abdul Hadi et al., 2013). Mixed method approach can be described as a process where the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study (Tashakkori & Creswell, 2007).

Greene, Caracelli & Graham (1989) identified five reasons for adopting mixed methods research including: triangulation of data to enrich the description about the problem and validate findings, expanding the understanding of the research problem, overcoming the limitations of using a single method, clarification of results from one method by using the results from the other method and to find paradox or contradiction of questions or results from one method with questions or results from another method for the purpose of highlighting new areas for investigation and/or reshaping the research question. Bryman (2006) added more possible reasons to conduct mixed methods research such as instrument development, to facilitate sampling for another study, uncovering relationships between variables through quantitative methods and then discovering their meaning through qualitative methods. In practice, there is typically more than one reason for the researcher to justify their choice of mixed method approach in their study (Abdul Hadi et al., 2013).

The selection of mixed methods approach for a study entails a range of advantages and shortcoming of both the qualitative and quantitative phases of the study. Evidence has shown that by mixing methods, the qualitative data was able to save quantitative data from being inaccurate or with limited value as it can highlight inconsistencies and could identify major issues that were not statistically significant (Weinholtz, Kacer & Rocklin, 1995; Smith, 1999). Using mixed methods could overcome the limitations of using qualitative or quantitative methods alone, provides more evidence about a research problem, helps answer questions that cannot be answered by a single method and gives the researcher more freedom in the use of all research methods available to address a research problem (Creswell & Plano Clark, 2011). However, the use of mixed methods was also associated with some criticism within the literature. Some have concerns about combining methods from different philosophical assumptions (i.e. positivist and realist) within the conceptual framework of a single study, particularly with qualitative and quantitative approaches (Smith, 1999). Mixed methods are a relatively new methodology and therefore may be challenging to enlighten and convince others of their usefulness (Creswell & Plano Clark, 2011). They have a wide range of designs, which could confuse new researchers in the field when they want to select the optimal design for their study (Leech & Onwuegbuzie, 2007). The previous studies associated with

mixed methods could also be difficult to locate within the literature because researchers only recently started to use the term mixed methods in their titles or in their methods section (Creswell & Plano Clark, 2011). On a practice level, mixed method studies could require more skill from both the qualitative and quantitative components of the study, more time and resources to use, and may require more researchers to conduct it when compared with using qualitative or quantitative studies alone (Abdul Hadi, Alldred, Closs & Briggs, 2014; Creswell & Plano Clark, 2011; Johnson & Onwuegbuzie, 2004; Doyle, Brady & Byrne, 2009).

Therefore, a mixed method design was chosen for this study in order to investigate medicine quality and their problems between the available facts and stakeholders' perceptions in two main phases within this study. The first phase involved a quantitative study to examine the possibility of medicine quality problems in terms of API quantity, authenticity of source and visual inspection of package regarding one popular antidiabetic medicine (glibenclamide) within a chosen healthcare sector (MOI-MSD) in Saudi Arabia. The second phase of the study explored the stakeholders' (i.e. commissioners, physicians, pharmacists and patients) perceptions about medicine quality and their problems within the same settings in the MOI-MSD in Saudi Arabia.

2.1.4 Quantitative phase of the study

The overall purpose of the quantitative approach is to generate reproducible findings that can be generalised to a wider population. The quantitative approach includes two major types of research known as survey and experimental research. The survey research provides a numeric description of trends, attitudes or opinions of a population by studying a large sample that is statistically significant. Experimental research is particularly useful for projects conducted in laboratory settings (Smith, 1999; Smith, 2005; Jesson & Pocock, 2001; Creswell, 2009).

The advantages in using a quantitative approach for research studies is in generalisability of findings, identifying factors associated with outcome, utility of an intervention and to understand the best predictors for an outcome. However, the limitation of this approach is the lack of flexibility to provide a true reflection of reality from different angles in a given situation. Furthermore, the quantitative approach does

not answer the "why?" and "how?" questions in contrast to the qualitative approach. This would therefore be of limited use in areas of research with an insufficient pre-existing body of knowledge on a given phenomena (Smith, 1999; Smith, 2005; Jesson & Pocock, 2001; Creswell, 2009).

Therefore, within the overall mixed method approach chosen for this study, the first phase adopted a quantitative approach since laboratory testing was based on recognised pharmacopoeial specifications that was required to answer the first research question. As shown in the first systematic review of the literature (Chapter 3), there were a large number of similar studies on a global scale that met the chosen inclusion criteria of focusing on prospective medicine field surveys of medicines. In addition to reinforcing the choice of approach for this phase of the study, the first systematic review (Chapter 3) had influenced the choice of variables to be examined, the type of instruments to be used and the gaps in current knowledge regarding therapeutic categories and geographical locations where little is known about the actual medicine quality and their problems.

2.1.5 Qualitative phase of the study

The qualitative approach is essentially related to the constructivist paradigm where it is exploratory in nature and aims to generate rather than test a hypothesis. Qualitative strategies explore and attempt to understand the meaning people ascribe to a social or human phenomena or problem. The number of samples and statistical significance is of limited use in this type of approach. Qualitative research is particularly useful when we do not know the variables to examine; the topic is new, if the topic has never been addressed in this population or when the existing theories do not apply to a specific population (Smith, 2005; Creswell, 2009).

Several types of research following the qualitative strategies can be identified including ethnography, grounded theory, case studies, phenomenology, narrative research and others. Ethnography is concerned with the study of culture groups in their natural settings in a flexible and evolving process over a prolonged period of time, collecting mostly observational and interview data. In grounded theory, the researcher develops a theory from participants' views by collecting data on multiple occasions and comparing

the data with emerging categories and theoretical sampling in an attempt to view similarities and differences between groups. Case studies explore in detail an activity, program, event, process or people by using various data collection tools over a sustained period of time. Phenomenology, which can be considered as a philosophy as well as a method, identifies a human experience about phenomena as described by a participant over a prolonged engagement time to develop patterns and relationships. Narrative research asks one or more people about their life stories, which is then retold by the researcher and combined with their own life story (Smith, 2005; Creswell, 2009). Within the context of this phase of the study, a case study strategy was employed to gather information from different MOI-MSD stakeholders within a limited time by using a variety of data collection tools.

The analysis of qualitative data follows similar steps to quantitative data analysis where both approaches start with organising raw data, entering and coding data, searching for the meaning of data through analysis, interpreting meaning and drawing conclusions. The main difference is that qualitative data analysis searches for meaning through thematic analysis while quantitative data analysis searches for meaning through statistical analysis. In addition, the steps of entering and coding data, data analysis and interpretation is much more close in qualitative data analysis while being distinctive steps in quantitative data analysis. The analysis of qualitative data could be inductive or deductive depending on the aim/objectives of the study and the available pre-existing knowledge on the subject (O'Leary, 2010; Kumar, 2011).

Therefore, within the overall mixed method approach chosen for this study, the second phase that was concerned with the stakeholders' perceptions about medicine quality and their problems, a qualitative approach was selected in order to explore these issues in-depth where little evidence is available in the pre-existing body of knowledge as was shown in the second systematic review of the literature in this study (Chapter 5). Moreover, a survey questionnaire was distributed to healthcare providers in the MOI-MSD settings as a part of this study to examine the issue through a wider range of healthcare providers.

Qualitative data can be collected through several methods including individual interviews, focus groups, direct observation and analysis of textual or visual data (Silverman, 2014). The interview research method could either be structured, semi-structured or unstructured. The structured interview method can be highly associated with quantitative strategies while semi-structured and unstructured interviews are associated with qualitative research strategies. The semi-structured interviews would have a number of questions within the interview schedule as a base for the study and allow probing and prompting answers from the participants in order to follow up on their interesting replies and clarify questions if needed (Bryman, 2012). The focus group allows for attitudes, opinions or perceptions about phenomena to be investigated through free and open discussions among a homogeneous group of no more than twelve participants. The researcher in a focus group discussion starts the process by raising issues or asking questions to stimulate the group discussion. It can be regarded as an inexpensive, easily designed and rapid source of valuable information. However, the drawbacks of using focus groups in a study needs careful attention from the researcher such as possible opinion domination of some individuals in the study and its incapability to find the magnitude of opinion diversity on a given issue (Krueger & Casey, 2009; Kumar, 2011). Furthermore, the direct observation of participants can be used to collect data in their natural settings (Mays & Pope, 1995). The analysis of texts or visual data can be performed by examining their content, coding of data and arranging them in themes or categories.

Consequently, a variety of qualitative methods including focus group, semi-structured interviews and survey questionnaires that included open-ended questions were used in the second phase of the study in order to explore the stakeholders' perceptions about medicine quality and their problems in the MOI-MSD in Saudi Arabia.

2.1.6 Framework of thesis

The framework of this thesis was a pragmatic framework and adopted a mixed method approach to investigate the perceived central research problem in order to address it in this study.

2.1.7 Thesis structure

The thesis includes eight chapters in total as shown in Figure 2.1.

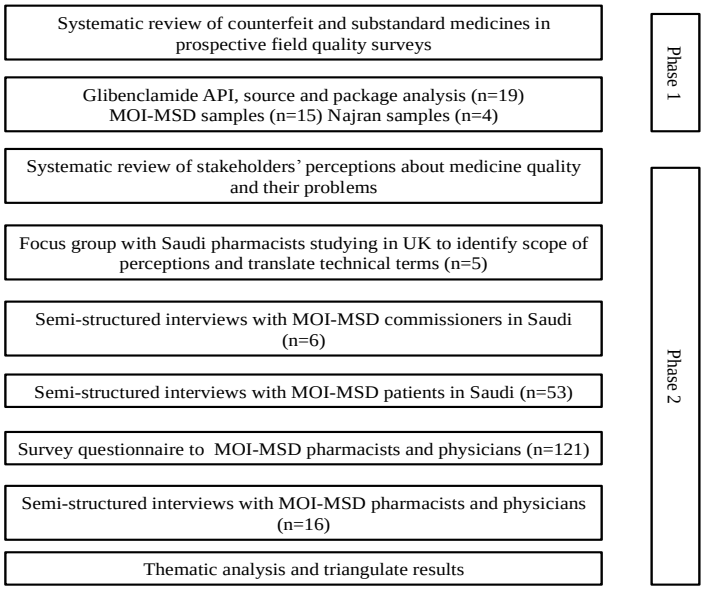


Figure 2.1 Overall methodology of the study

2.1.8 Phase one of the study

The first phase of the study started with a systematic review of the literature to determine existing gaps in knowledge about prospective field quality surveys which investigated the issue of counterfeit and substandard medicines. Based on the findings of this systematic review, limited studies have addressed these issues with chronic medicines worldwide, only a few studies were identified in the Middle East and none in Saudi Arabia. Therefore, it became evident that a study was needed to explore the possibility of counterfeit and substandard medicines in Saudi Arabia by focusing on specific variables and analysis types that were extracted from the systematic review results. Subsequently, chemical analysis of glibenclamide samples collected from the MOI-MSD in Saudi Arabia were analysed in the laboratory to examine the amount of API in comparison with USP specification and samples from community pharmacies in Najran, in addition to authentication of source, and the visual inspection of packaging information.

2.1.9 Phase two of the study

The second phase of the study was also initiated with a systematic review of the literature to examine existing studies on stakeholders' perception about medicine quality and related problems. The findings from this systematic review demonstrated the scarcity of research studies that addressed these issues worldwide and the absence of such studies in Saudi Arabia. Furthermore, it was found that none of the studies explored the perceptions of commissioners, healthcare providers and patients in a single setting and none explored perceptions about medicine quality and related problems in one study. Therefore, it was necessary to address these gaps in knowledge by conducting a study to explore these issues. The first phase of this study included a focus group study with Saudi Arabian pharmacists in the United Kingdom (UK) to generate ideas regarding the development of questions and Arabic translation of technical terms such as counterfeit medicines to be implemented in the following phases of this study. The second and third phases of this study explored the perceptions of commissioners and patients respectively in MOI-MSD in Saudi Arabia through semi-structured interviews. The fourth phase of this study investigated the perceptions of pharmacists and physicians in MOI-MSD by distributing a survey questionnaire that included open and closed-ended questions. This was followed by the fifth and final phase that confirmed the answers obtained from the survey questionnaires and further explored some issues raised by the pharmacists and physicians. Subsequently, common and specific themes were identified from all stakeholders' groups and their results were discussed.

2.1.10 Summary

A summary of the research questions, methodology, rationale and methods used in the thesis can be found in Table 2.1.

Table 2.1 Summary of research questions, methodology, rationale and methods in the study

First phase			
Research questions	**Methodology**	**Rationale**	**Methods**
Are there any SSFFC medicines in the glibenclamide samples collected from MOI-MSD in Saudi Arabia?	Quantitative	Determine API quantity, source authenticity and package information of glibenclamide samples	HPLC (USP standards) WHPA/FIP checklist for visual inspection Official reception documents comparison with available medicines
What are the characteristics and nature of SSFFC Glibenclamide samples in MOI-MSD Saudi Arabia, if found?	Quantitative	Report any problems found in API quantity, source authenticity or packaging information	HPLC (USP standards) WHPA/FIP checklist for visual inspection Official reception documents comparison with available medicines
Second phase			
What are the perceptions of commissioners, healthcare professionals and patients in MOI healthcare services about the medicine quality and related problems?	Qualitative	Explore evidence and triangulate findings regarding medicine quality and counterfeit medicines from different stakeholders' perspectives	Focus group Semi-structured interviews Survey questionnaire Thematic analysis Descriptive analysis
What is the knowledge and behaviour associated with medicine quality and related problems among healthcare employees and patients in MOI health services?	Qualitative	Explore evidence and triangulate findings regarding medicine quality and counterfeit medicines from different stakeholders' perspectives	Focus group Semi-structured interviews Survey questionnaire Thematic analysis Descriptive analysis

2.2 Methodology

2.2.1 General method

This study used a mixed method approach and was carried out in two phases as previously discussed. The first phase started with a systematic review about counterfeit and substandard medicines in field quality surveys and was then followed by the analysis of glibenclamide samples. The second part of the study started with a systematic review regarding stakeholders' perceptions about medicine quality and substandard or counterfeit medicines and was then followed by investigation of the perceptions of MOI-MSD stakeholders by using a series of methods including focus group discussion, semi-structured interviews and questionnaire survey in Saudi Arabia.

2.2.2 Phase one

2.2.2.1 Study design

A quantitative research approach using a cross-sectional survey method was adopted in this phase of the study. The researcher collected fifteen glibenclamide samples overtly from MOI-MSD general warehouse in Riyadh and a research assistant collected four glibenclamide samples covertly from community pharmacies in Najran for comparison. All samples were kept in plastic bags arranged in a box where they were kept at room temperature and away from light for one week before being sent via a logistics company to the United Kingdom for analysis.

2.2.2.2 Study settings

The glibenclamide samples from MOI-MSD were collected prospectively from the general warehouse by the researcher in August 2013. A research assistant collected samples from Najran community pharmacies prospectively in September 2014.

2.2.2.3 Study sample

A total of 19 glibenclamide samples were available for analysis in this phase of the study. Glibenclamide was selected for the purpose of this phase of the study since diabetes affects a large proportion of the Saudi Arabian population (Salman & Al-Rubeaan, 2009; Eledrisi et al., 2007) and had the largest volume of demand in MOI-MSD at the time of the study design as discussed in Chapter 4. The number of samples

required was estimated to be five samples from each available batch in the MOI-MSD general warehouse based on previous literature to account for natural variations between medicine packages of the same batch (Phanouvong & Blum, 2004) and the WHO guidelines for sampling medicines (WHO, 2005). It was found that three different batch numbers from the same supplier were available at the time of sample collection and therefore fifteen samples in total were collected from MOI-MSD settings. Furthermore, four more samples from Najran community pharmacies were conveniently available for comparison purposes in this phase of the study. These samples were from four different manufacturers in order to obtain a snapshot about the quality of glibenclamide commercially available to MOI-MSD patients in case of glibenclamide non-availability in the MOI-MSD clinics.

2.2.2.4 Data collection

A random sampling strategy based on a systematic approach was employed to collect the required samples from MOI-MSD general warehouse in order to collect five samples from each available batch number at one point in time. Moreover, the research assistant collected samples from Najran conveniently from one community pharmacy in each area of the city at first sight.

2.2.2.5 Data analysis

The analysis process started with the authentication of source performed by the researcher for samples collected from MOI-MSD by on-site inspection of official reception documents with what was physically available in the warehouse. Following the shipment of glibenclamide samples to the UK, visual inspection of samples was performed using a tool kit developed by The World Health Professions Alliance (WHPA) and The International Pharmaceutical Federation (FIP) for visual inspection of medicines (FIP, 2013). Subsequently, chemical analysis of glibenclamide samples for API quantity was conducted in the laboratory using HPLC, according to USP specifications.

2.2.2.6 Validity and reliability

The chemical and visual data analysis of glibenclamide was based on recognised methods of the USP and WHPA/FIP respectively. Furthermore, in order to increase the

reliability of API concentration results, samples were injected in duplicates into the HPLC system and the mean of the results was reported.

2.2.3 Phase two

2.2.3.1 Study design

This phase of the study was further divided into five phases. The first phase was a focus group discussion with Saudi Arabian pharmacists studying in the UK in order to explore the scope of perceptions about medicine quality and related problems to compose the question design of the study in addition to translating technical terms such as counterfeit medicines into Arabic for subsequent parts of the study. The second and third phases of the study explored the perceptions of MOI-MSD commissioners and patients respectively about medicine quality and related problems through semi-structured and face-to-face interviews with open-ended questions. The fourth phase of this study investigated the MOI-MSD primary clinic physicians' and pharmacists' perceptions about medicine quality and related problems through a survey questionnaire that was distributed electronically and manually to healthcare providers and included open-ended and closed-ended questions. The fifth phase of the study validated and further explored in-depth the results from the fourth phase of the study through semi-structured interviews with pharmacists and physicians in the MOI-MSD, being conducted via recorded telephone calls with the participants. Subsequently, results from all phases were triangulated and discussed to identify similarities and differences in perceptions about medicine quality and their problems from the different stakeholders' perspectives in MOI-MSD settings in Saudi Arabia.

2.2.3.2 Study settings

The focus group phase of the study was conducted in the University of Hertfordshire settings in the UK. The semi-structured interviews with the commissioners were conducted in their offices at the MOI-MSD general administration in Riyadh, Saudi Arabia. The interviews with patients were conducted in two MOI-MSD primary clinics in Riyadh and one primary clinic in Jeddah, Saudi Arabia. The survey questionnaire was distributed to all MOI-MSD pharmacists and physicians in primary care clinics in the country, as well as to pharmacists working in the Medical Supply Department at the MOI-MSD General Administration in Riyadh, Saudi Arabia. Furthermore, the

telephone interviews with MOI-MSD healthcare providers were conducted with pharmacists and physicians working in different cities in Saudi Arabia.

2.2.3.3 Study sample

The focus group phase of the study included Saudi Arabian pharmacists, studying for post-graduate qualification during the academic year 2013/2014 at the University of Hertfordshire in the UK, who agreed to participate in the study. Convenient sampling was used to recruit pharmacists in this phase of the study in order to achieve the study objectives. Although this sampling approach could be bias, it was necessary to map the scope of pharmacists' perceptions about medicine quality and their problems since it was not possible to identify other Saudi Arabian stakeholders in the UK at the time of the study. The commissioners of MOI-MSD were individually identified and approached in this study based on their professional role as decision makers in the pharmaceutical supply chain in MOI-MSD settings. Patients were randomly approached for recruitment in three MOI-MSD primary clinics, as they are the ultimate users of medicines with the only exception being younger patients under the age of 18 years old. Pharmacists and physicians in MOI-MSD primary clinics were recruited for the survey questionnaire and the following interviews via the commissioner of their department at the MOI-MSD general administration in Riyadh, Saudi Arabia, as they are responsible for medicine dispensing and prescribing respectively.

2.2.3.4 Data collection

The collection of data at the different phases of the study followed receipt of the participant information leaflet, signature of an informed consent form, and provision of their demographic details. The focus group part of the study was conducted in December 2013 and was completed in 93 minutes. The interviews with MOI-MSD commissioners were performed in their offices in March 2014 and none lasted more than 30 minutes. Interviews with MOI-MSD patients were conducted in vacant physicians' offices in each setting to protect their privacy in the period between March to April 2014 and none lasted more than 30 minutes. The survey questionnaire was distributed to MOI-MSD physicians and pharmacists in March 2014 and the web-based version was available online for eight weeks. The telephone interviews with MOI-MSD pharmacists and physicians were conducted in December 2014 and none lasted more

than 50 minutes. Furthermore, with the exception of survey questionnaire completion and telephone interviews with MOI-MSD physicians and pharmacists, data was collected within normal working hours between 8 am and 2 pm in Saudi Arabia, and 9 am and 5 pm in the UK on the previously discussed dates.

2.2.3.5 Translation

The focus group and the survey questionnaire phases of the study were conducted in English while interviews with commissioners, patients, physicians and pharmacists were conducted in Arabic. At the start of this study, the focus group participants translated technical terms such as counterfeit medicines into Arabic for the subsequent parts of the study. Survey questionnaires were distributed in English since they were aimed at healthcare providers only and therefore they would have sufficient English proficiency to complete these questionnaires. Commissioners were considered knowledgeable individuals in this study and therefore the interviews with them were conducted in Arabic to allow for more in-depth exploration of their perceptions. In contrast, patients could have low literacy levels and, therefore, interviews were conducted in Arabic in an attempt to simplify the process of exploring their perceptions. The follow-up telephone interviews with pharmacists and physicians were performed in Arabic to allow the participants to express their opinions freely by minimising any possible language barriers resulting from using English in the previous questionnaire phases of the study with the same stakeholders.

The process of translating questions and transcripts into English, when Arabic was used, followed the same principle of back translation at the different phases of the study. The questions were translated to Arabic by the principal researcher; then translated to English and back to Arabic by two different bilingual native Arabic speaking members of staff at the University of Hertfordshire and the two versions of the Arabic questions in the interview guide were compared. Furthermore, following the transcription and translation of the Arabic interviews, two bilingual native Arabic speaking members of staff at the University of Hertfordshire assisted the principal researcher in validating the accuracy of translation from two randomly chosen interview transcripts.

2.2.3.6 Data analysis

The data analysis for the focus group and the interview phases of the study started with the transcription of data into a Microsoft Word document, assigning a unique identifying code for each participant, the translation of data into English and the validation of translation, when required, before conducting thematic analysis. The thematic analysis of data was conducted using NVivo, version 10, where codes were developed in order to generate themes and sub-themes. The researcher extracted the themes and sub-themes and his supervisor performed trustworthiness checks at the end of each phase of the study.

For the questionnaire survey part of the study, data was analysed using Microsoft Excel and SPSS version 21 software. The responses to open-ended questions were analysed using Microsoft Excel through a content analysis approach, and their results shown as numbers and percentages. The responses to closed-ended questions were descriptively analysed using SPSS for both categorical and continuous data, where association between some variables was examined, and the findings reported as numbers and percentages.

2.2.3.7 Reliability

The reliability of findings was addressed in this phase of the study by having a structured and documented process of data collection and analysis. Furthermore, the research supervisor independently coded at least two interviews from each part of the study and then met with the researcher to compare sets of codes and resolve any disagreement in coding by discussion of the issues.

2.2.3.8 Validity

The validity was addressed through a series of steps at different stages of this phase of the study. The questions design was based on findings of the systemic review about stakeholders' perceptions on medicine quality and their problems in addition to findings from the focus group study. Subsequently, questions for the following phases of the study were designed and checked for face validity by three members of academic staff at the University of Hertfordshire. Before collecting data at each part of the study, the questions were piloted with at least two individuals, who were not part of the study

sample, to ensure the questions' content, clarity, order and time required to complete. The interview transcripts were sent back to participants for their review where possible, excluding patients who only provided telephone numbers for contact in order to receive their comments and feedback. Moreover, the themes and sub-themes extracted from the different phases of the study were triangulated and the researcher's supervisor reviewed and verified the interview coding and results to address the internal validity.

2.2.3.9 Generalisability

This phase of the study was exploratory in nature and therefore did not seek generalisability of findings for the Saudi Arabian population. Nevertheless, this phase of the study did explore the perception of six commissioners and more than fifty individuals from each group of pharmacists, physicians and patients in MOI-MSD settings in Saudi Arabia. Future research could address the issue of generalisability, based on the findings from this phase of the study.

3 Chapter 3: A systematic review of counterfeit and substandard medicines in field quality surveys

3.1 Introduction

Medicine safety, efficacy, and quality are the most important criteria in ensuring optimal treatment from medicines and are currently receiving increased attention in an era of globalisation and generic manufacturing (Waller, 2001; Amin et al., 2005). Medicines with questionable quality could either be counterfeit or substandard, according to the World Health Organisation (WHO). A counterfeit medicine is defined by the WHO as "one which is deliberately and fraudulently mislabeled with respect to identity and/or source." Counterfeiting could include both branded and generic products and may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging (WHO, 1999a). Substandard medicines, also referred to as out-of-specification products, are defined by the WHO as "products that do not meet the required specification in terms of content and ingredients" (WHO, 2003a; WHO, 2014). They are legally manufactured but do not conform to specifications as a result of inadequate manufacturing or poor storage conditions (Heyman et al., 2011; Yankus & Marks, 2009; Wertheimer & Norris, 2009; Clift, 2010). Recently, the term substandard/spurious/falsely labeled/falsified/counterfeit medicines (SSFFC) was used by the WHO to simultaneously describe both counterfeit and substandard medicines (Deats & Bourdillon-Esteve, 2013). This joint definition highlights the importance of identifying both counterfeit and substandard medicines in any proposed medicine quality survey.

The distinction between counterfeit and substandard medicines is imperative when applying appropriate strategies to combat potential threats of either quality problem (Newton et al., 2009; Newton et al., 2011). However, some dismiss this notion and argue that both counterfeit and substandard medicines are similar because they both claim to be something that in reality they are not (Amin & Kokwaro, 2007). Nevertheless, correctly identifying the type of medicine quality problem could aid

governments and responsible bodies in determining the need to involve local or international law enforcement, particularly when scarce economic resources are present. Counterfeit medicines are strongly linked with organised crime and would most likely require criminal experts to aid health care professionals to combat this problem, as demonstrated by the establishment of the International Medical Products Anti-Counterfeiting Taskforce to support the WHO efforts to combat counterfeit medicines globally (WHO, 2011).

Medicine quality problems could be fatal in extreme clinical outcomes and have also been associated with severe economic consequences. More than 700,000 deaths from tuberculosis and malaria have been strongly linked with ineffective counterfeit and substandard medicines worldwide (Cockburn et al., 2005; Mackey & Liang, 2011). Mortality has also been reported after heparin contamination in the United States and sexual enhancement drugs adulterated with large contents of hypoglycemic drugs in Singapore (Kao et al., 2009; Lühn et al., 2011; Davison, 2011; Holzgrabe & Malet-Martino, 2011). Moreover, substandard and counterfeit medicines have been related to morbidity, drug resistance, therapeutic failure, and toxicity (Wertheimer & Norris, 2009; Amin & Kokwaro, 2007; Cockburn et al., 2005; Mackey & Liang, 2011). Economically, substandard and counterfeit medicines have been suggested to cause macroeconomic burdens worldwide by wasting limited resources, causing loss of productivity, and limiting investment of major pharmaceutical companies into medicine research and development (Yankus & Marks, 2009; Wertheimer & Norris, 2009; Moken, 2003). Furthermore, consequences of substandard and counterfeit medicines could result in loss of confidence in health care professionals and/or services (Wertheimer & Norris, 2009; Amin & Kokwaro, 2007; Cockburn et al., 2005; Mackey & Liang, 2011).

The WHO estimates that around 10% of all global pharmaceutical supply is counterfeit and substandard, reaching up to 50% of the supply in developing countries and as low as 1% in the developed world (Heyman et al., 2011; Cockburn et al., 2005; Ziance, 2008). These estimates cannot be a reliable estimate of the true extent of the problem since the available literature on the subject is limited; the existing studies used different methodologies and sampling techniques. Therefore, it is imperative to interpret any

estimates of SSFFC medicines prevalence rate with extreme caution. Moreover, it has been suggested that the majority of reported SSFFC medicines were substandard, rather than counterfeit, yet they receive far less attention within the media and the scientific community (Caudron et al., 2008; Fried, 2011).

The aim of this systematic review is to broadly explore the evidence of substandard and counterfeit medicines in scientific reports to identify current knowledge limitations and provide an overview report of the current situation. Previously, some reviews have focused on specific medicine categories or problems (Amin & Kokwaro, 2007; Caudron et al., 2008; Newton, Green, Fernández, Day & White, 2006; Nayyar, Breman, Newton & Herrington, 2012). Only one review comprehensively searched for substandard and counterfeit medicine articles covering the period from 1966 to 2006 without specifying a therapeutic medicine category (Kelesidis, Kelesidis, Rafailidis & Falagas, 2007). Recently, the first systematic review on the subject of counterfeit and substandard medicines was published (Almuzaini et al., 2013). However, Almuzaini et al have only reviewed some articles from a single therapeutic class that demonstrated high-quality reporting, which could be useful in the determination of SSFFC prevalence rates but may not be comprehensive enough to describe the broad scope and nature of SSFFC medicines available in other reports. Further, the previous systematic review did not discuss the types of analysis performed in the included studies, nor did it identify therapeutic classes or global regions in which the quality of medicines remains largely unknown. This review attempts to cover these issues broadly to encourage future researchers on medicine quality to focus their attention on neglected medicines and neglected parts of the globe. Furthermore, this review discusses types of analysis currently performed in medicine quality surveys to identify areas of concern and to promote the consideration of counterfeit as well as substandard medicines when conducting any medicine quality survey.

3.2 Methods

3.2.1 Searching the literature

Scopus, PubMed, and ISI Web of Knowledge databases have been searched for relevant

research articles. The search covered the period from 1997, the year the first relevant citation was found, up to December 31, 2013. There was no language restriction applied on our search results.

The following key search terms were used in conjunction, using (AND) to identify related articles: substandard(s) or counterfeit(s); medicine(s) or drug(s) or pharmaceutical(s). The choice of key search terms was based on key search terms used in five previous literature reviews (Amin & Kokwaro, 2007; Caudron et al., 2008; Newton et al., 2006; Nayyar et al., 2012; Kelesidis et al., 2007). The main distinction of our present review compared with most previously published reviews is its systematic nature and broader scope, as no medicine groups or settings were specifically chosen in the search terms and inclusion criteria used.

The definitions and criteria used to describe counterfeit and substandard medicines in this review are based on the widely accepted WHO definitions of each phenomenon, as cited earlier (WHO, 1999a; WHO, 2003a; WHO, 2014). On the basis of the WHO criteria, a counterfeit medicine could be determined by chemical analysis methods if medicine samples contained no, or the wrong, active ingredient. A counterfeit medicine could also be identified via medicine package analysis by visual comparison to a known genuine package. Other means of detecting counterfeit medicines include authenticating its source through official consignment documents or communication with the stated manufacturer and regulatory organisations. In addition, deliberately manufactured substandard medicines are considered counterfeit, although this would be difficult to demonstrate without legal and criminal investigation by authorities. In contrast, a substandard medicine should always contain the correct active pharmaceutical ingredient (API), be produced from a legitimate source, and be without packaging defaults. Substandard medicines are present when the amount of API is outside the acceptable pharmacopoeial limits, the sample does not meet other standards set by the pharmacopoeias, or medicines are past their expiry dates. Collectively, we refer to both counterfeit and substandard medicines as SSFFC medicines, in accordance with the latest WHO joint definition (Deats & Bourdillon-Esteve, 2013).

3.2.2 Inclusion and exclusion criteria for articles in this review

Studies included in this review were original research articles that reported prospective medicine sample collection from their natural settings; these medicines were presumed to be readily available to patients. Further, all included articles must have reported conducting chemical tests for the identification and/or quantification of the API. Without performing chemical analysis, it would not be possible to determine whether a medicine sample was counterfeit or not, as no information on the API would be present. In addition, relevant studies would include medicine samples from a wide range of different therapeutic categories and dosage forms without any restrictions.

In contrast, the exclusion criteria of articles would include studies that did not report primary collection of medicine samples or medicines procured from the Internet or retrospectively collected through authority or innovator company seizures. Furthermore, studies that reported only physical or packaging testing without chemical analysis were excluded. Duplicate results and nonrelevant articles were also identified and excluded from this review.

3.2.3 Data presentation of articles in this review

This systematic review has been performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews (Moher et al., 2009). All percentages of SSFFC medicines available in this review are reported as cited from their primary source. Therefore, caution is advised, as methodological differences exist between articles. The data presented here do not allow for any estimation of the SSFFC prevalence rate worldwide.

3.3 Results

3.3.1 Data extraction

The use of the selected search terms resulted in a total of 3,861 hits from all databases. An initial screening of titles/abstracts followed this, excluding nonrelevant and duplicate results to reduce the number of results to 1,288 research articles. Subsequently, a full review of articles was performed that further excluded articles without primary data collection, such as reviews and opinions, articles containing retrospective sample collection of medicines (either donated or seized by authorities), medicines acquired through the Internet, nonrelated articles, studies without medicine sample collection, and studies that did not perform chemical analysis of samples. This strategy reduced the final number of the included articles to 66. A flowchart illustrating the method used for article selection in this review and different exclusion categories is shown in Figure 3.1.

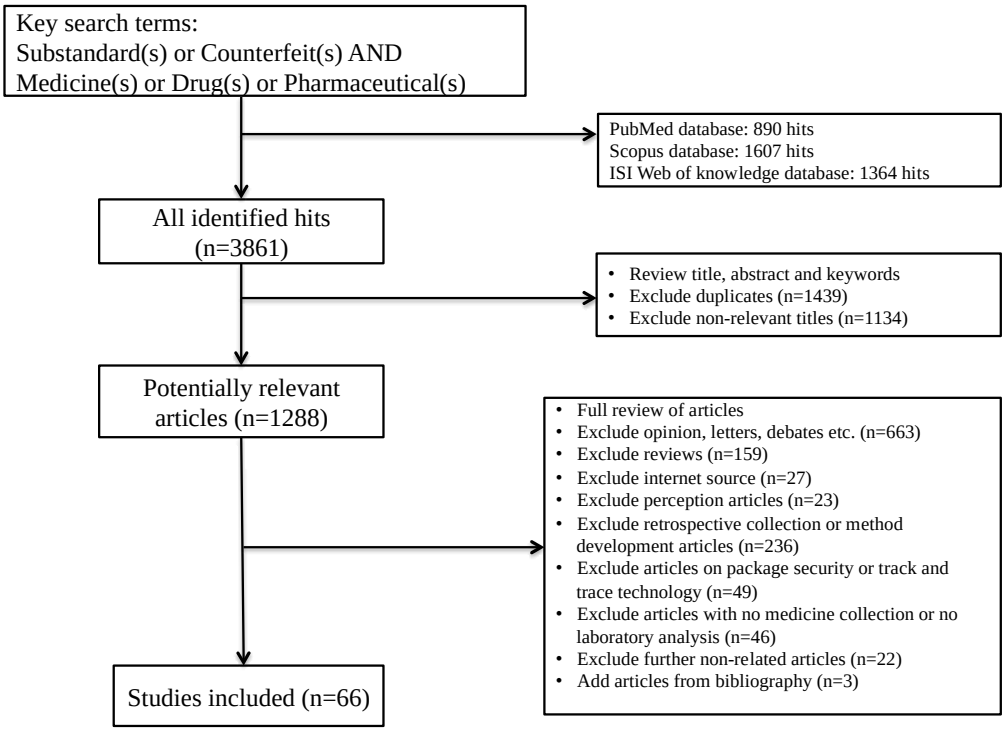


Figure 3.1 Flow chart for articles inclusion in the first systematic review

3.3.2 Location of included studies

The majority of reported studies prospectively examining SSFFC medicines were conducted in the African continent (31/66; 47%). Nigeria and Ghana alone were selected for more than 50% (17/31) of the studies in Africa (Tables 3.1, 3.2 and 3.4). In Asia, 23/66 (35%) of the SSFFC medicine quality surveys were conducted, mostly in the South Eastern part of Asia (Tables 3.1-3.4). Eight research articles were performed in the southern parts of the continent in Pakistan, Bangladesh, and India (Tables 3.1, 3.2 and 3.4). Overall, only two studies (3%) were published that addressed SSFFC medicines in the western part of Asia, also known to be part of the Middle East (Table 3.4). Elsewhere, 6/66 (9%) of studies were conducted in more than one continent simultaneously (Tables 3.1, 3.2 and 3.4). Moreover, three studies were performed in North/South America (4%) and two in Eastern Europe (3%) (Table 3.4). Only one study was located in the borderline area between Asia and Australia in Papua New Guinea (Table 3.1).

3.3.3 Medicine therapeutic classes in included studies

Substandard and counterfeit medicines were found from various therapeutic categories. However, most SSFFC studies 57/66 (86%) were focused on medicines that treat infectious diseases. Antimalarial, antibiotic, and antituberculosis medicines were examined in 30/66 (46%), 10/66 (15%), and 5/66 (8%) of the located studies, respectively (Tables 3.1, 3.2, and 3.4). The combination of more than one class of medicines to treat infectious diseases was found in 12/66 (18%) of the articles (Baratta et al., 2012; Nair et al., 2011; Bate et al., 2009b; Risha et al., 2008; Pouillot, Bilong, Boisier, Moumouni & Nabeth, 2008; Syhakhang et al., 2004; Taylor et al., 2001; Shakoor et al., 1997; Bate et al., 2011; Seear et al., 2011; Bate et al., 2009a; Kayumba et al., 2004). Other infectious diseases such as leishmaniasis medicines were investigated on one (2%) other occasion (Dorlo et al., 2012). In contrast, medicines for treatment of noncommunicable diseases were present in only 9/66 (14%) of the cited literature (Stanton et al., 2012; Baratta et al., 2012; Syhakhang et al., 2004; Said et al., 2011; Haruna, Adaku & Usifoh, 2013; Audu et al., 2012; Karlage et al., 2012; Twagirumukiza et al., 2009; Fotiou, Aravind, Wang & Nerapusee, 2009). The analgesic paracetamol was investigated on two separate occasions (Baratta et al., 2012; Said et al., 2011).

Similarly, antihypertensive medications were surveyed in only two studies (Haruna, et al., 2013; Twagirumukiza et al., 2009). Nonsteroidal anti-inflammatory agent aspirin was analysed in one further study (Syhakhang et al., 2004). The antihistamine medicine chlorpheniramine was only present in one survey (Audu et al., 2012). Narrow-therapeutic index medicines also were the focus of only one published study (Karlage et al., 2012). Other types of medicines such as ergometrine, oxytocin, and erythropoietin appeared in only one study each (Stanton et al., 2012; Fotiou et al., 2009). A single study attempted to collect samples from various therapeutic categories simultaneously (Baratta et al., 2012).

3.3.4 Evidence and nature of SSFFC medicines

Overall, substandard medicines were found in the majority of prospective SSFFC medicine studies (60/66; 91%) (Tables 3.1 and 3.4). Counterfeit medicines were less evident in 29/66 (44%) of available studies (Tables 3.1 and 3.2). Counterfeit and substandard medicines were simultaneously found in 24/66 (36%) articles (Table 3.1). Few studies 5/66 (8%) reported only evidence of counterfeiting in the medicine samples collected (Table 3.2). Evidence of medicines being only substandard, rather than counterfeit, was found in 36/66 (55%) of the articles (Table 3.4). One study did not find evidence of counterfeit or substandard medicines in their sample (Table 3.3).

Several types of SSFFC problems have been reported in the selected literature. It was noted that more than one medicine quality problem typically exists within each prospective medicine quality survey (Tables 3.1, 3.2, and 3.4). The most reported medicine quality problem was failure to comply with the specified API limits in 46/66 (70%) of cases (Tables 3.1 and 3.4). Failure of dissolution or disintegration tests has been reported in 24/66 (36%) of the articles (Tables 3.1 and 3.4). The presence of either no API (Newton et al., 2011; Stanton et al., 2012; Baratta et al., 2012; Nair et al., 2011; Ochekpe, Agbowuro & Attah, 2010; Bate et al., 2009a; Tipke et al., 2008; Pouillot et al., 2008; Atemnkeng, De Cock & Plaizier-Vercammen, 2007; Gaudiano et al., 2007; Syhakhang et al., 2004; Basco, 2004; Dondorp et al., 2004; Taylor et al., 2001; Stenson, Lindgren, Syhakhang & Tomson, 1998; Shakoor et al., 1997; Dorlo et al., 2012; Sengaloundeth et al., 2009; Newton et al., 2008) or the wrong API (Newton et al., 2011; Onwujekwe et al., 2009; Prazuck et al., 2002; Sengaloundeth et al., 2009) was reported

in 20/66 (30%) and 4/66 (6%) cases, respectively. Other problems were also reported, including fake package (Ochekpe et al., 2010; Newton et al., 2001), fake hologram (Newton et al., 2011; Newton et al., 2008; Newton et al., 2001), manufacturer does not exist (Newton et al., 2011; Nair et al., 2011; Atemnkeng et al., 2007), manufacturer confirmed a nonauthentic batch (Khan et al., 2010; Newton et al., 2008), expired medicines (Stanton et al., 2012; Prazuck et al., 2002; Pribluda et al., 2012), no origin country stated (Taylor et al., 2001), no manufacturer address (Nair et al., 2011; Ali et al., 2011; Ofori-Kwakye, Asantewaa & Gaye, 2008), no manufacturer stated (Atemnkeng et al., 2007), no expiry date (Ali et al, 2011; Bate et al., 2008; Prazuck et al., 2002), unusual interval between manufacturing and expiry date (Sengaloundeth et al., 2009), wrong name on package or leaflet (Newton et al., 2011), wrong spelling of "tablet" (Sengaloundeth et al., 2009; Newton et al., 2008), use of a different font (Newton et al., 2008), different medicinal taste (Newton et al., 2001), heavier weight (Newton et al., 2001), nonauthorised manufacturer (Lon et al., 2006), absence of trade name (Atemnkeng et al., 2007), signs of deterioration (Shakoor et al., 1997), and diverted medicines (Gaudiano et al., 2007; Fotiou et al., 2009) intended for distribution in one location and found to be on sale in another market.

3.3.5 Type of analysis identified in the included studies

Four distinctive types of analysis can be used to distinguish between a genuine and SSFFC medicines; namely, authentication of the supplier, visual package inspection, and chemical and physical analysis (Tables 3.1–3.4). Authentication of the medicine source via contact with manufacturer, health regulatory agencies, or Internet search has been only attempted in 10/66 (15%) of the selected studies (Tables 3.1, 3.2, and 3.4). Package inspection was more popular than authentication, being reported in 39/66 (59%) of studies, with the majority reporting obvious spelling errors and basic label information (medicine name, dosage, manufacturer, expiry date, and lot number), as shown in Tables 3.1, 3.2, and 3.4. As for the chemical analysis, high-performance liquid chromatography and thin-layer chromatography (TLC) were most widely used in 40/66 (61%) and 19/66 (29%) of studies, respectively (Tables 3.1, 3.2, and 3.4). Other chemical analysis methods were reported such as color reaction tests, spectroscopic techniques and titration but remain less frequently used (Tables 3.1–3.4).

Moreover, physical analysis tests were performed in 39/66 (59%) of the studies (Tables 3.1, 3.2 and 3.4). The most common physical tests reported were disintegration and/or dissolution tests in 36/39 (92%) cases (Tables 3.1, 3.2, and 3.4). Other less frequently used physical analysis tests include content uniformity (Tables 3.1 and 3.4), weight measurement (Tables 3.1, 3.2, and 3.4), hardness (Tables 3.1 and 3.4), and friability tests (Tables 3.1 and 3.4). Interestingly, only six studies (9%) reported all four types of analysis in an attempt to clearly identify and classify the type of SSFFC problem, where present, in any medicine sample (Tables 3.1 and 3.4).

Table 3.1 Research articles reporting both counterfeit and substandard medicines

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Bate et al. (2013)	17 countries from all continents	Anti-TB isoniazid and rifampicin	713	NR	Package	TLC	Disintegration	65/713 (9.1%) substandard 18/713 (2.5%) counterfeit	Low API% No API or suspicious packaging
Stanton et al. (2012)	Ghana	Ergometrine Oxytocin	101	NR	NR	Performed by local FDA	NR	92/101 (91%) substandard 1/101 (1%) counterfeit	Low or high API% 2 expired No API
Baratta et al. (2012)	15 different countries	Various therapeutic classes and formulations	196	NR	NR	UV and some with HPLC-UV	Uniformity of content, mass, disintegration, friability and hardness tests	101/196 (52%) substandard 4/196 (2%) counterfeit	Various failures mostly physical No API
Nair et al. (2011)	Papua New Guinea	Antimalarial amodiaquine and antibiotic amoxicillin	14	Internet search and e-mail contact manufacturer	Package and label inspection	TLC and HPLC-UV	Weight variation, content uniformity, dissolution	11/14 (79%) substandard 3/14 (11%) counterfeit	Poor content uniformity, fails assay and inappropriate packaging No API, no manufacturer address and distributor does not exist
Ali et al. (2011)	Nigeria	Antimalarial ACT	6	NR	Package inspection	UV	NR	3/6 (50%) substandard 2/6 (33%) counterfeit	Low API% Missing manufacturer details on package and no expiry date
Khan et al. (2010)	Cambodia	Albendazole, mebendazole and metronidazol	203	Contact with manufacturer and authorities	Package inspection	HPLC-UV	Disintegration and weight measurement	2% substandard 4% counterfeit	Failed disintegration Failed authenticity with manufacturer or authorities
Ochekpe et al. (2010)	Nigeria	Antimalarial artemisinin combination therapies	70	NR	Package inspection Minilab®	TLC	Disintegration	27/70 (38%) substandard 4/70 (6%) counterfeit	Low API% No API and fake packaging
Bate et al. (2009a)	India	Antimalarial, antibiotic and antimycobacterial	541	NR	NR	TLC	Disintegration	46/541 (8.5%) substandard 11/541 (2%) counterfeit	Low API% and disintegration failure No API

Table 3.1 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Onwujekwe et al. (2009)	Nigeria	Antimalarial	225	NR	NR	HPLC-UV	Dissolution	60/225 (37%) substandard or counterfeit	Less API% or wrong API
Risha et al. (2008)	Tanzania	Antimalarial, Antibiotic and antiretroviral	1257	NR	Package inspection Minilab®	Colour reaction and TLC	Disintegration test and dissolution	46/1257 (3.6%) substandard 5/1257 (0.4%) counterfeit	Dissolution failure mostly NR
Tipke et al. (2008)	Burkina Faso	Antimalarial	77	Internet search was for manufacturers	Package inspection Minilab®	Colour reaction and TLC	Disintegration	32/77 (42%) substandard 1/77 (1.2%) counterfeit	Failed visual inspection, low AP% and failure of dissolution test No API
Bate et al. (2008)	6 African countries	Antimalarial	210	NR	Package inspection	TLC	Dissolution	35% (73/210) substandard 7/210 (3%) counterfeit	Low API% and dissolution failure Missing manufacturing and/or expiry date on the package
Pouillot et al. (2008)	Cameroon and Niger	Antimalarial, antibiotic and antithelmentic	153	NR	Basic package inspection	HPLC-UV	Average weight and uniformity of mass, disintegration dissolution	66/153 (43%) substandard 5/153 (3%) counterfeit	Non-conforming to API% and physical tests No API
Ofori-Kwakye et al. (2008)	Ghana	Antimalarial artesunate	17	NR	Basic package inspection	Colorimetric and spectrometry	Uniformity of weight, breaking strength, friability and rate of disintegration	11/17 (65%) substandard 1/17 (6%) counterfeit	Failed content uniformity test Manufacturer address missing
Atemnkeng et al. (2007)	Congo	Antimalarial	28	NR	Package inspection	UV, TLC and HPLC-UV	NR	4/28 (14%) substandard 13/28 (46%) counterfeit	Low and high API% No API, no manufacturer name and no trade name
Gaudiano et al. (2007)	Congo, Burundi and Angola	Antimalarial	30	NR	Package and label	HPLC and photo-diode array	Uniformity of mass, disintegration and dissolution	17/30 (57%) substandard 1/30 (3%) counterfeit 1/30 (3%) diverted	Low API% and physical test failures No API Humanitarian medicine

Table 3.1 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Atemnkeng et al. (2007)	Kenya and Congo	Antimalarial Artemisinin-derivative drugs	24	Checked source of some companies	Check for illegal prints only	HPLC-UV	NR	9/24 (38%) substandard 3/24 (12.5%) counterfeit	Low and high API% Non-existent manufacturer
Syhakhang et al. (2004)	Laos (two studies in 1997 and 1999)	Antibiotic, antimalarial and aspirin	666	NR	NR	HPLC-UV and titration	Weight variation and disintegration	46% and 22% substandard in 1997 & 1999 1% counterfeit	Low or high API% and failed weight variation t No API
Basco (2004)	Cameroon	Antimalarial	284	NR	NR	Colour test and TLC	NR	53/284 (18%) substandard 59/284 (20%) counterfeit	Low API% No API
Dondorp et al. (2004)	Thailand, Vietnam, Cambodia, Laos PDR and Myanmar	Antimalarial artesunate derivatives and mefloquine	303	NR	Package analysis of holograms	Colour test and HPLC with photo-diode array	NR	99/303 (33%) counterfeit 4/303 (1%) substandard	No or trace API and all were artesunate Substandard API % and all were mefloquine
Prazuck et al. (2002)	Myanmar	Antibiotics	21	NR	NR	UV, TLC and titrimetry	NR	10/21 (48%) substandard 3/21 (14%) counterfeit	Low, high API% and expired medicines Wrong API and no expiry date on package
Taylor et al. (2001)	Nigeria	Antimalarial, antibiotic, anti TB, antifungal	581	NR	Basic package information on origin	HPLC-UV	NR	279/581 (48%) substandard 43/581 (7%) counterfeit	Low API% No API and no origin country on package
Stenson et al. (1998)	Laos	Antibiotics ampicillin and tetracycline	366	NR	Basic visual analysis	Colour test, TLC, HPLC-UV and titration	Measurement of weight variation	42/366 (11.5%) substandard 12/366 (3.3%) counterfeit	Low or high API% and weight variation No API
Shakoor et al. (1997)	Nigeria and Thailand	Antimalarial and antibiotics	96	NR	Package inspection for obvious errors	HPLC-UV	NR	36% from Nigeria and 40% from Thailand substandard 6/96 (6%) counterfeit	Low or high API% and signs of decomposition No API

Table 3.2 Research articles reporting counterfeit medicines only

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Dorlo et al. (2012)	Bangladesh	Miltefosine	2	NR	Package inspection	LC-MS, FT-IR, NIR, colorimetric test	NR	Both (100%) failed all tests and are counterfeit	No API
Newton et al. (2011)	Multiple countries in Africa	Antimalarial	59	Contact manufacturer	Package inspection	HPLC with photo-diode array and other tests	NR	Only case reports of counterfeits and do not allow for percentage estimation	Wrong API, non-existent manufacturer, no API, hologram different from genuine package and wrong name on packaging or leaflet
Sengaloundeth et al. (2009)	Laos	Antimalarial artesunate	30	NR	Package analysis	Colorimetric tests, HPLC-mass spectroscopy, pollen analysis, X-ray diffraction	NR	88% failure and counterfeit	No or wrong API, wrong spelling of "tablet" on package and unusual interval between manufacturing date and expiry date of nine years
Newton et al. (2008)	Vietnam, Cambodia, Myanmar, Laos and Thailand	Antimalarial artesunate	391	Contact with one company to authenticate batch numbers	Package analysis including holograms	Colorimetric, HPLC-mass spectrometry	NR	195/391 (50%) counterfeit	Fake hologram, wrong spelling on packaging, use of different font, failure of authentication when manufacturer was contacted and no API
Newton et al. (2001)	Myanmar, Cambodia, Vietnam, Laos, and western Thailand	Antimalarial artesunate	104	NR	Package inspection and holograms, printing and bar codes	Colour reaction test	Tablet weight, size and colour	Overall 38% are counterfeit found in all countries	No API, different taste of tablets, heavier weight of tablets and different packaging and holograms compared to genuine

Table 3.3 Study with no report of substandard or counterfeit medicines

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results
Said et al. (2011)	Malaysia	Paracetamol	16	NR	NR	NIR spectroscopy	NR	All samples passed but with variable quality

Table 3.4 Research articles reporting only substandard medicines

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Haruna et al. (2013)	Nigeria	Antihypertensive Methyldopa	4	NR	NR	Non-aqueous titration	NR	1/4 (25%) substandard	Low API%
Audu et al. (2013)	Congo	Antihistamine chlorpheniramine	10	NR	NR	HPLC-UV	Tablet shape, size, thickness and weight. Disintegration and friability tests	3/10 (30%) substandard	Low API%
Ramachandran et al. (2013)	India	Anti-TB	1948 tablets	NR	NR	Spectrometry	NR	168/1948 (9%) substandard	Low and high API%
Khan et al. (2013)	Cambodia	Antibiotic amoxicillin-clavulanic acid	59	Contact with manufacturer and local authorities	Basic visual analysis of primary and secondary packaging	HPLC-UV	Stability and dissolution	12/59 (20%) substandard	Low API%, failure of content uniformity and dissolution tests
Affum et al. (2013)	Ghana	Antimalarial artesunate and amodiaquine	32 blisters	NR	Basic visual analysis and compared to genuine	Titrimetric and HPLC-UV	Tablet weight	14/32 (43.75%) substandard	Low and high API% mostly artesunate
Briesen et al. (2012)	Kenya and Congo	Antibiotic eye drops	33	NR	NR	HPLC-UV	NR	19/33 (58%) substandard	Low and high API%
Nogueira et al. (2012)	Brazil	Antimalarial medicines	9	NR	Simple package analysis	HPLC-UV	Dissolution, disintegration, hardness, uniformity of weight and friability tests	4/9 (44%) substandard	Failing only visual inspection and uniformity of weight
El-Duah & Ofori-Kwakye (2012)	Ghana	Antimalarial artemisinin-medicines	14	NR	For illegal print errors	Colorimetry and TLC	Uniformity of mass, crushing strength and disintegration	13/14 (93%) substandard	Low or high API% and failing physical tests
Karlage et al. (2012)	Mexico	Antibiotics, warfarin, levothyroxine and sildenafil	17	NR	NR	HPLC-UV	Weight measurement	5/17 (30%) substandard	Low API%

Table 3.4 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Pribluda et al. (2012)	Seven countries in South America	Antimalarial	1663	NR	Package and label	TLC	Disintegration	193/1663 (11%) substandard	Expired medicines mostly, low API% and failure of disintegration tests
Klein et al. (2012)	Ghana	Antimalarial	33	NR	Package inspection	NMR	NR	1/33 (3%) substandard	Low API%
Ehianeta et al. (2012)	Nigeria	Antimalarial artesunate and amodiaquine combination	13	NR	Package inspection of expiry date and registration	HPLC-UV	NR	11/13 (85%) substandard	Low and high API%
Bate et al. (2011)	17 countries from all continents	Antimalarial, antibiotics and anti-TB	899	NR	Package inspection	TLC and Raman	Disintegration	15% substandard	Failure of visual inspection, low API% and dissolution failure
Seear et al. (2011)	India	Ciprofloxacin, Artesunate and Rifampicin	300	NR	NR	HPLC-MS	NR	43% substandard	Low and high API%
Akpabio et al. (2011)	Nigeria	Antibiotic ciprofloxacin	4	NR	NR	Titration	Uniformity of weight, hardness, disintegration, dissolution and friability	1/4 (25%) substandard	Low API%, failure of friability and dissolution tests
Hadi et al. (2010)	Indonesia	5 different Antibiotics	104	NR	Package inspection	HPLC-UV	NR	18% substandard	Low API%
Bate & Hess (2010)	Ghana and Nigeria	Antimalarial	339	NR	Package inspection	TLC and Raman	Disintegration	23% substandard	Failure of visual inspection, low API% and dissolution failure
Leslie et al. (2009)	Pakistan	Antimalarial	9	NR	NR	HPLC-UV	Dissolution	100% substandard	High API% and dissolution failure

Table 3.4 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Twagirumukiza et al. (2009)	Rwanda	Antihypertensive drugs	10	NR	NR	HPLC-UV	Dissolution	2/10 (20%) substandard	Low and high API%
Obaid (2009)	Pakistan	Antibiotic ceftriaxone injection	96	NR	NR	HPLC-UV	NR	15/96 (16%) substandard	Low and high API%
Bate et al. (2009b)	Ghana, India, Kenya, Nigeria, Tanzania, and Uganda	Antimalarial, antibiotic and antimycobacterial	78	NR	NR	TLC, NIR and Raman	Disintegration	40/78 (51%) substandard	Low API% and disintegration failure
Fotiou et al. (2009)	Thailand	Epoetin alfa-prefilled syringes	139	Checked batch numbers with manufacturer	Primary and secondary package and security features	HPLC-UV and HPLC-MS	NR	32/139 (23%) substandard and diverted	Exceeded specific content requirement for the product and batch number matches products sold outside the country according to the manufacturer
Kaur et al. (2008)	Tanzania	Antimalarial	304	NR	NR	HPLC-UV	Dissolution	12.5% substandard	Low API% and dissolution failure
Kyriacos et al. (2008)	Lebanon, Syria, Jordan, Egypt and Saudi Arabia	Amoxicillin antibiotic in different formulations	111	NR	NR	HPLC-UV	NR	56% of capsules substandard 8% of suspensions substandard	Low API%
Moes et al. (2008)	Estonia and Russia	Antibiotic doxycycline	8	NR	Basic package inspection	HPLC-UV	Dissolution	2/8 (25%) substandard	Low API% and dissolution failure

Table 3.4 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Bronnikova et al. (2007)	Estonia and Russia	Antibiotic amoxicillin	6	NR	Basic package inspection	HPLC-UV	Dissolution	1/6 (16%) substandard	Dissolution failure
Vijaykadga et al. (2006)	Thailand	Antimalarial	369	NR	Package and label	TLC and HPLC-UV	Disintegration	23/369 (6%) substandard	Low API% and disintegration test failure
Lon et al. (2006)	Cambodia	Antimalarial	451	One company was investigated by contact with local authorities	Visual inspection Minilab®	TLC	Disintegration	122/451 (27%) substandard	Low API% and disintegration test failure One illegal manufacturer identified
Amin et al. (2005)	Kenya	Antimalarial	116	NR	Package and storage area inspection	HPLC-UV	Dissolution	47/116 (40%) substandard	Low API% and dissolution failure
Abdo-rabbo et al. (2005)	Yemen	Antimalarial tablet and syrup	50	NR	NR	HPLC-UV	Dissolution	16/50 (32%) substandard	Low API%, high API% and dissolution failure
Rookkapan et al. (2005)	Thailand	Anti-TB	52	One quality report was requested from a manufacturer	Tablet inspection	HPLC-UV	Dissolution	37% substandard	Failure of visual inspection, low API% and dissolution failure
Kayumba et al. (2004)	Rwanda and Tanzania	Antimicrobial and antimalarial drugs	33	NR	NR	HPLC-UV	Dissolution	4/33 (12%) substandard	Dissolution failure
Minzi et al. (2003)	Tanzania	Antimalarial	33	NR	Basic package information	TLC and HPLC-UV	Dissolution	12/33 (36%) substandard	Low API% and dissolution failure

Table 3.4 Continued

Reference	Country	Medicine(s)	Sample size	Authenticate source	Visual analysis	Chemical analysis	Physical analysis	Results	Type of SSFFC problem
Obodozie et al. (2003)	Nigeria	Antibiotic in different formulation	22	NR	NR	HPLC-UV	NR	9/22 (41%) substandard	Low and high API%
Laserson et al. (2001)	7 different countries	Anti-TB	71	NR	Basic package information	TLC and LC-MS	NR	10% substandard	Low API%
Kenyon et al. (1999)	Botswana	Anti-TB Fixed dose combination (FDC)	13	NR	NR	TLC, LC and UV	NR	4/13 (31%) substandard	Low and high API%

Table 3.5 Prevalence of reported SSFFC problems in some studies

Continent	Country	Reference	Range of SSFFC reported problems (%)
Africa	Nigeria	Ali et al. (2011)	33%-50%
		Ochekpe et al. (2010)	6%-38%
		Onwujekwe et al. (2009)*	37%
		Taylor et al. (2001)*	7%-48%
		Shakoor et al. (1997)*	6%-36%
		Haruna et al. (2013)	25%
		Ehianeta et al. (2012)	85%
		Akpabio et al. (2011)	25%
		Obodozie et al. (2003)	41%
	Ghana	Stanton et al. (2012)	1%-9%
		Ofori-Kwakye et al. (2008)	6%-65%
		Affum et al. (2013)	43%
		El-Duah & Ofori-Kwakye (2012)	93%
		Klein et al. (2012)	3%
	Tanzania	Risha et al. (2008)	3%
		Kaur et al. (2008)*	12%
		Minzi et al. (2003)	36%
	Burkina Faso	Tipke et al. (2008)	1%-42%
	Congo	Atemnkeng et al. (2007)	14%-46%
		Audu et al. (2013)	30%
	Cameroon	Basco (2004)*	18%-20%
	Rwanda	Twagirumukiza et al. (2009)	20%
	Kenya	Amin et al. (2005)	40%
	Botswana	Kenyon et al. (1999)	31%
	Multiple countries	Bate et al. (2008)	3%-35%
		Pouillot et al. (2008)	3%-43%
		Gaudiano et al. (2007)	3%-57%
		Atemnkeng et al. (2007)	12%-38%
		Bate & Hess (2010)	23%

*High quality studies found in Almuzaini et al. (2013)

Table 3.5 Continued

Continent	Country	Reference	Range of SSFFC reported problems (%)
Asia	Papua New Guinea	Nair et al. (2011)	11%-79%
	Cambodia	Khan et al. (2010)	2%-4%
		Khan et al. (2013)	20%
		Lon et al. (2006)*	27%
	India	Bate et al. (2009a)	2%-8%
		Ramachandran et al. (2013)	9%
		Seear et al. (2011)	43%
	Laos	Syhakhang et al. (2004)*	1%-46%
		Stenson et al. (1998)	11%
		Sengaloundeth et al. (2009)	88%
	Myanmar	Prazuck et al. (2002)	14%-48%
	Thailand	Shakoor et al. (1997)*	6%-40%
		Fotiou et al. (2009)	23%
		Vijaykadga et al. (2006)	6%
		Rookkapan et al. (2005)	37%
	Bangladesh	Dorlo et al. (2012)	100%
	Malaysia	Said et al. (2011)	0%
	Indonesia	Hadi et al. (2010)*	18%
	Pakistan	Leslie et al. (2009)	100%
		Obaid (2009)	16%
	Yemen	Abdo-rabbo et al. (2005)	32%
	Multiple countries	Dondorp et al. (2004)*	1%-33%
		Newton et al. (2001)	38%

		Kyriacos et al. (2008)	56%
South America	Brazil	Nogueira et al. (2012)	44%
	Multiple countries	Pribluda et al. (2012)	11%
North America	Mexico	Karlage et al. (2012)	30%
Europe	Estonia and Russia	Moes et al. (2008)	25%
	Estonia and Russia	Bronnikova et al. (2007)	16%

*High quality studies found in Almuzaini et al. (2013)

3.4 Discussion

3.4.1 Neglected parts of the world in SSFFC surveys

According to our findings, the vast majority of prospective medicine quality studies were conducted in small parts of Africa and Asia. These efforts can be attributed to an attempt to counteract nonexistent or lower levels of regulation in these pharmaceutical markets (WHO, 2010a). However, some parts of these two continents still have limited scientific research addressing the problem of SSFFC medicines, mainly in the Middle East and North Africa. In Yemen, 32% of selected antimalarial medicines failed analysis tests, and the majority of these were substandard, having lower than accepted API% limits and unacceptable dissolution rates (Abdo-Rabbo et al., 2005). Another study explored the API content of the antibiotic amoxicillin purchased from Egypt, Lebanon, Jordan, and Saudi Arabia and found that more than 50% of samples had lower API% than accepted by pharmacopeial limits, and therefore were considered substandard (Kyriacos et al., 2008). A multicountry medicine quality survey found that 12% of samples collected from Egypt failed at least one medicine quality test and can be considered substandard (Bate et al., 2011). None of these studies reported an attempt to verify the source or analyse packages of the selected medicine samples to explore the possibility of counterfeiting activity. This may cause some concern, particularly with recent seizures of SSFFC medicines in this area. In addition, the currently unsettled political situation may be a catalyst for the increased prevalence of SSFFC medicines, as it allows them to escape immediate governmental attention (McGinnis, 2013). Reports of recent seizures of SSFFC medicines in this area can be mostly found in the

media, which remains the main source of information regarding SSFFC medicines in this region with limited published scientific reports (McGinnis, 2013). Moreover, a WHO report on questionnaire responses from a number of health organisations in the Eastern Mediterranean Regional Office regarding counterfeit medicines has confirmed counterfeit seizures in this region by some respondent countries (WHO, 2010b). In addition, this area could be of specific importance in terms of geographical location, as it separates two well-established regions of SSFFC medicine prevalence, according to our data, and is en route between potential counterfeit manufacturers in Asia (Newton et al., 2008) and their global targeted markets. It is therefore suggested that several pilot studies be conducted to survey the quality of medicines in the Middle East and North Africa to assess the current medicine quality situation before any countermeasures or large-scale medicine quality surveys can be recommended. Elsewhere, in developing countries such as India, Pakistan and Thailand, pilot studies have been shown to be instrumental in the assessment of the medicine quality situation in different countries and to have justified the need for further medicine quality surveys, where appropriate (Bate et al., 2013; Bate et al., 2009b; Newton et al., 2001; Obaid, 2009).

Evidence from South America suggests that SSFFC medicines are available, but with only limited scientific research. A study found 11% of antimalarials to be substandard in seven South American countries using basic TLC chemical analysis (Pribluda et al., 2012). The TLC analysis technique is limited by its inability to detect higher than 80% of API concentration in medicine samples (Bate et al., 2008) which has been evident to exist in previous studies (Stanton et al., 2012; Bate et al., 2008; Atemnkeng et al., 2007; Prazuck et al., 2002; Stenson et al., 1998; Shakoor et al., 1997; Ramachandran et al., 2013; Affum et al., 2013; El-Duah & Ofori-Kwakye, 2012; Ehianeta et al., 2012). It is therefore possible that the prevalence of SSFFC medicines in South America could be higher than the reported figures if more sophisticated chemical techniques for the quantification of API% content were used, such as high-performance liquid chromatography. Another study reported problems with low API% on a range of medicines procured from Mexico; of particular importance are some narrow therapeutic index medicines such as warfarin and levothyroxine (Karlage et al., 2012). Two studies from Eastern Europe found some problems regarding low API% and dissolution failures when a limited number of antibiotics were analyzed in Estonia and Russia (Meos et al.,

2008; Bronnikova et al., 2007). No studies could be identified that addressed medicine quality problems in the Australian continent.

3.4.2 Neglected noncommunicable medicines in SSFFC surveys

Most of the studies in this review were found to explore medicines used to treat infectious diseases such as malaria and tuberculosis. Medicines used to treat noninfectious diseases, also known as noncommunicable disease (NCD) medicines or chronic disease medicines, were only found in a few studies that presented some medicine quality problems (Stanton et al., 2012; Baratta et al., 2012; Syhakhang et al., 2004; Said et al., 2011; Haruna et al., 2013; Audu et al., 2012; Karlage et al., 2012; Twagirumukiza et al., 2009; Fotiou et al., 2009). However, on a global scale, NCDs and their medicines must not be ignored. The WHO estimates that NCDs kill more than 36 million people each year, of which 29 million deaths (80%) occur in low- and middle-income countries (WHO, 2013b). The currently available literature on medicine quality does not reflect the wider use of NCDs and their medicines globally, including in lower-income countries. This issue needs to be addressed rapidly, as recent evidence from Pakistan reported the death of more than 100 people after the administration of the antianginal medicine isosorbide mononitrate contaminated with large amounts of pyrimethamine (WHO, 2012b; Nishtar, 2012). Elsewhere, the US Food and Drug Administration recently issued warnings regarding counterfeit cancer medicines (FDA, 2012a, FDA, 2012b). Furthermore, evidence of counterfeiting involving NCD medicines such as diabetes treatments were found in illicit or lifestyle drugs, which may have significant implications for the public health and could result in death (Kao et al., 2009; WHO, 2012a; Lung, Gerona, Wu & Smollin, 2012). Therefore, it is recommended that we extend the attention of future medicine quality surveys globally beyond infectious diseases medicines and on to NCD medicines (and widely available treatments of diabetes and cardiovascular diseases in particular), in addition to cancer treatments and narrow therapeutics index medicines, as they could have severe health implications for the affected population.

3.4.3 Type of analysis used in SSFFC surveys

All studies included in this review performed chemical analysis for the identification and/or quantification of the API available in selected samples, in accordance with our

methodological approach. High-performance liquid chromatography and TLC were the most widely used chemical analytical techniques available in the selected articles, possibly because of their wide acceptance in the academic field and their application in many pharmacopoeial references. It is suggested that this would be a logical and possibly important consideration for future scholars interested in conducting medicine quality surveys to ensure the acceptance of their findings within the academic field.

Physical analysis tests were performed to complement chemical analysis in approximately 2/3 of the selected studies particularly disintegration and dissolution tests for solid dosage forms. This can be attributed to the availability of specific physical tests in different pharmacopoeias in addition to the use of physical information about the medicinal product to predict the bioavailability of medicines (Amin et al., 2005; Gaudiano et al., 2007; Rookkapan et al., 2005). However, such physical analysis tests could only be used as a bioavailability indicator and cannot substitute lengthy and expensive bioavailability studies (Kayumba et al., 2004; Kenyon et al., 1999). Moreover, it is important to note that performing physical analysis only on medicinal samples can be considered inadequate if the objective of the study was to determine medicine quality issues since it cannot be determined if the correct API and its quantity is present in medicine samples as specified in the WHO definition of substandard and counterfeit medicines (WHO, 1999a; WHO, 2003a; WHO, 2014).

Package inspection is another popular type of medicine analysis that was also found in nearly two-thirds of the medicine quality surveys in this review. On the basis of primary and secondary package information, the majority of reports seek obvious spelling errors, suspicious holograms compared with known genuine samples, and basic label misinformation such as medicine name, dosage, manufacturer details, expiry date, and lot number (Tables 3.1, 3.2, and 3.4). The WHO definition of counterfeit medicines highlights packaging information significance and could have influenced the wide use of package information among medicine quality surveys (WHO, 1999a). Furthermore, packaging information of medicines has been a valuable mode of analysis in the relevant literature and has revealed many counterfeit medicines that have passed chemical identification tests (Ali et al., 2011; Bate et al., 2008; Ofori-Kwakye et al.,

2008). A tool kit developed by the World Health Professions Alliance and the International Pharmaceutical Federation for visual inspection of medicines can be used for a systematic package inspection by health care professionals and scholars both in practice and in future investigative projects (FIP, 2013).

A less common level of analysis available in the literature is the authentication of medicine source via contact with the medicine manufacturer and local or international health authorities. This systematic review has identified only ten research articles that attempted to authenticate the source of the medicine samples (Nair et al., 2011; Khan et al., 2010; Tipke et al., 2008; Khan et al., 2013; Lon et al., 2006; Rookkapan et al., 2005; Newton et al., 2008; Atemnkeng et al., 2007; Newton et al., 2011; Fotiou et al., 2009). Perhaps researchers may not guarantee adequate responses to their queries from other parties, as some have suggested (Nair et al., 2011; Khan et al., 2010). It could also be possible that authenticating the source may not be within the scope of a particular medicine quality survey, as it could be only focused on substandard medicines issue (Taylor et al., 2001). Nevertheless, the WHO definition of counterfeit medicines clearly describes the deliberate and fraudulent misrepresentation of the medicine source as a characteristic of a counterfeit medicine (WHO, 1999a). Moreover, according to the Pharmaceutical Security Institute, counterfeit medicines are currently increasing in terms of reported incidences worldwide and can no longer be ignored (PSI, 2014a). It is recognised that obtaining authentication confirmation of medicine sources could be difficult in studies collecting samples from street markets; however, this task could be less complex when samples are collected from pharmacies or hospitals, as official records and documentation of medicines are expected to exist. Furthermore, according to the limited studies that reported authentication analysis in this review, many counterfeit cases were found by confirmation from manufacturers or health authorities of a nonauthentic batch of medicines, even if samples contained the correct API when chemically analysed (Khan et al., 2010; Atemnkeng et al., 2007; Lon et al., 2006).

Overall, there were very few research articles that performed all four levels of analysis: chemical, physical, package inspection, and authentication of source (Nair et al., 2011; Khan et al., 2010; Tipke et al., 2008; Khan et al., 2013; Lon et al., 2006; Rookkapan et al., 2005). Future medicine quality surveys are advised to consider performing all four

types of analysis for a more holistic approach, and equally, to address the possibility of finding either counterfeit or substandard medicines during an investigation. Further, it was noted that none of the medicine quality surveys examined patient information leaflets within medicinal packages to check for accuracy and up-to-date information made available to patients. Some studies, particularly in the Middle East, have found disagreement between patient information leaflets in some medicine samples when compared with national formularies (Gebran & Al Haidari, 2006; Al-Aqeel, 2012). Therefore, the addition of patient information leaflets to examination of medicine samples in medicine quality survey studies is open for debate among the scientific community.

3.4.4 Prevalence of SSFFC

Our data suggest that reports of substandard medicines are more widely available in the literature, particularly medicines with incorrect API% and failure of dissolution/disintegration tests, than counterfeit medicine reports (Tables 3.1–3.4). These findings are in line with previous reports that suggested that substandard medicines are more prevalent than counterfeits and require more global attention (Caudron et al., 2008; Fried, 2011). This phenomenon might be attributed to poor manufacturing practices or extreme weather conditions in some countries, accompanied by inadequate storage conditions (WHO, 2003a; WHO, 2014; Kyriacos et al., 2008). However, because the majority of cited articles in this review did not conduct authentication processes via contact with manufacturers and/or health authorities, as previously mentioned, medicine counterfeiting remains a possibility that has not been largely explored. Hence, considering the available data, it cannot be determined whether substandard medicines are indeed more prevalent than counterfeit medicines at this time. Future medicine quality researchers are therefore encouraged to remain vigilant about counterfeiting possibility and conduct all types of analysis including chemical, physical, package inspection, and authentication efforts to determine the type of medicine quality problem more accurately.

3.4.5 Limitations of this review

This systematic review is not without limitations. Articles conducting chemical analysis were a prerequisite for inclusion in this review. It focused only on prospective field

quality surveys and excluded reporting of any studies with retrospective or previously seized SSFFC medicines in the literature. The rationale for excluding studies with retrospective medicine sampling is that they do not imitate natural settings of medicine procurement and typically aim to propose new methods of analysis rather than predict the prevalence rate of SSFFC in different markets. The Internet source of medicines was beyond the scope of our review. Relevant articles from the bibliographical list of available studies were only included on some occasions and cannot be considered exhaustive. The included articles were not assessed for the quality of their methodology, which was found to vary considerably among the selected articles. No attempt was made to calculate prevalence rates of SSFFC medicines or test for statistical significance, as it would have resulted in the exclusion of most articles from this review, as most reported studies used convenience sampling and/or with limited sample size (Newton et al., 2009).

3.4.6 Strengths of this review

This review has several strengths. To the researcher's knowledge, it is only the second systematic review on the subject of SSFFC medicines. Evidence of SSFFC medicines in terms of nature and type of analysis were discussed. This information would most likely aid government agencies and health care authorities and scientists interested in the medicine quality issues in developing or improving current policies and practices. It was the intention of this review to help interested parties identify and describe SSFFC medicine problems with up-to-date scientific evidence. Further, this review highlighted neglected medicine types and neglected geographical location in terms of scientific research addressing SSFFC medicines. This could invite more research projects addressing these neglected medicines and geographical locations to improve current knowledge on the issue and maintain patient safety. Moreover, this review has identified the limited scientific research, conducting field quality surveys on SSFFC medicines, using all four levels of analysis, in an attempt to encourage future researchers to explore all possibilities when conducting a medicine quality survey in any settings.

3.5 Conclusion

The problem of SSFFC medicines is evident worldwide. Potential harm to patients' health requires global collaboration exceeding the status quo. Limited research addressing SSFFCC medicines was noted in several parts of the world, including the Middle East, North Africa, and Australia. Similarly, more research is required to address SSFFC medicines from noncommunicable medicine classes, including narrow therapeutic index and chronic medicines, as current scientific knowledge regarding these medicines remains limited despite their popularity and media reports of the existence of SSFFC medicine problems in such therapeutic classes. Furthermore, the current focus of published research on chemical and physical analysis of medicine samples could overlook the possibility of counterfeiting if additional steps of analysis were performed, including package inspection and authentication of source via contact with manufacturers and health authorities. Future medicine quality surveys are encouraged to perform all four levels of analysis to explore all possibilities of substandard and counterfeit medicines that may be present in their selected sample of medicines. Such an approach would be beneficial in determining the type and prevalence rate of medicine quality problems in any setting and could consequently determine the most appropriate strategies to combat their threats.

4 Chapter 4: Glibenclamide quality analysis

4.1 Background

Poor quality medicines can be defined as medicine with quality problems such as counterfeit, substandard or degraded medicines (Newton et al., 2009; Newton et al., 2011). For generic medicines, others propose that quality problems may also include medicines that are not bioequivalent, contain insufficient information in patient information leaflet, do not offer substantial price reduction and are not generally accepted by patients (Asiri & Al-Yamani, 2006).

Glibenclamide, also known as glyburide in the United States, is a sulfonylurea oral hypoglycemic medicine that stimulates the beta cells' release of endogenous insulin from the pancreas and has been used by Type two diabetic patients for generations (Luzi & Pozza, 1997). It has been described as the most extensively used medicine for type two diabetic patients in many parts of the globe (Nanovskaya, Nekhayeva, Hankins & Ahmed, 2006).

Despite the perceived low price of glibenclamide, which might not be clearly attractive for counterfeiters in terms of price per unit, it could be a target in terms of mass volume since counterfeit glibenclamide has been found in Brazil (da Silva Fernandes, da Costa, Valderrama, Marco & de Lima, 2012). On other occasions, street drugs have been found to contain counterfeit glibenclamide, which resulted in severe health implications on some individuals and on extreme cases and may have resulted in their death (Lung et al., 2012; Lim et al., 2009).

4.2 Aim and objectives

The overall aim of this study is to evaluate the quality of glibenclamide medicine samples available in the MOI-MSD settings.

The objectives of this study include:

1) Establish whether any selected glibenclamide medicine samples fail API quantity chemical tests, visual tests and verification of source where possible.

2) To describe the nature of any glibenclamide failed samples, if found.

4.3 Selection of glibenclamide for quality analysis

The consideration was given to a medicine with the highest potential impact on a large population in Saudi Arabia. The prevalence of diabetes in Saudi Arabia is estimated to be 24% of the adult population, which presents a significant challenge for the government (Salman & Al-Rubeaan, 2009; Eledrisi et al., 2007). This is not only in provision of health care but also financially. Medicines for the treatment of chronic conditions such as diabetes and cardiovascular diseases have been shown to be of high volume and demand in MOI-MSD healthcare settings (Table 4.1). Moreover, findings of a recent study within MOI hospital found that 16% of diabetic patients receiving oral hypoglycemic medicines were unsatisfied with their treatment and 54% of them were interested in changing their medicine (Al-Aujan, Al-Aqeel, Al-Harbi & Al-Abdulltif, 2012). Therefore, the choice of the oral hypoglycemic medicine glibenclamide, which had the highest amount of ordered quantities and potential use, was considered for the purpose of this study.

Table 4.1 High-volume diabetes and CV medicines available from GPP tender in the MOI-MSD in Saudi Arabia

Medicine	**Pharmacological Class**	**Manufacturer**	**Annual order (tablet)**	**Price per tablet (USD)**	**Total annual expenditure (USD)**
Glibenclamide 5 mg tablet	Sulfonylurea Hypoglycemic	Kuwait Saudi (Kuwait)	8,000,000	0.0062	49,600
Acetyl Salicylic Acid 75-100 mg tablet	NSAID	Julphar (UAE)	6,400,000	0.0105	67,200
Metformin 500 mg tablet	Biguanide Hypoglycemic	Gulf Pharm. Ind. (UAE)	3,500,000	0.0103	36,050

Atenolol 50 mg tablet	Beta Blocker	National Pharm. (Oman)	1,600,000	0.0065	10,400
Amlodipine 5 mg capsule	Calcium Channel Blocker	Tabouk (KSA)	1,200,000	0.0065	7,800
Lisinopril 10 mg tablet	ACE inhibitor	Pharma Intl. (Jordan)	1,200,000	0.0093	11,160
Atorvastatin 10 mg tablet	Cholesterol lowering agent	Tabouk (KSA)	1,100,000	0.0140	15,400

*Based on MOI-MSD data for medicines available in the year 2013

4.4 Context of this study (MOI-MSD)

The setting chosen for this study is the MOI-MSD Primary Care Clinics (PCC). There are three major primary clinics in Riyadh and 18 PCC in other regions of the country that provide healthcare to approximately 2 million patient visits each year (Table 4.2). Employees of the MOI and their families are eligible to free healthcare services in these PCCs, including free prescription and over the counter medicines. Typically, these PCCs are the first point of contact with patients, and any critical cases that require further secondary care can be referred to MOI-MSD secondary care hospital in the capital city Riyadh. Although both the hospital and PCC serve the same patients, each has its own method of medicine procurement. The PCCs generally acquire their medicines from the GPP tender, particularly high volume medicine to utilise price reductions available through the programme. This joint programme involves participants from all ministries of health in the gulf countries and other governmental healthcare providers in Saudi Arabia as discussed earlier. Medicines are usually delivered from the awarded manufacturer or agent to the MOI-MSD general warehouse in Riyadh in two or three shipments throughout the year. It is then distributed to all PCCs around the country. Therefore, it was thought that the MOI-MSD general warehouse in Riyadh would be an ideal location for sample collection as it serves as the first point of receiving of medicines from the manufacturers before distribution to all

PCCs around the country. Table 4.2 lists all MOI-MSD PCC in Saudi Arabia according to their region and illustrates the number of annual patient visits at each site. Appendix 3 further demonstrates the location of MOI-MSD PCC in different regions on the geographical map of Saudi Arabia.

Table 4.2 MOI-MSD primary care clinics statistics (official 2014 statistical report currently in publishing)

Location	**City or PCC name**	**Annual number of patients**	**Percentage of all PCC patients**
Riyadh city	Riyadh Polyclinics	13704	0.7%
	Training City	23935	1.2%
	Security College	100195	5%
Central Region	Alkharj	34725	1.8%
	Hail	69634	3.5%
	Qassim	111570	5.6%
Northern Region	Aljouf	101803	5.1%
	Alqoriat	43656	2.1%
	Northern Borders	99267	5%
	Tabouk	58340	3%
Western Region	Jeddah	137197	7%
	Medina	153984	7.8%
	Mecca	205771	10.3%
	Taif	99003	5%
Eastern Region	Ahsa	123971	6.2%
	Dammam	115444	5.9%
Southern Region	Albaha	87151	4.3%
	Asir	93183	4.7%
	Bisha	79433	4%
	Jizan	159700	8%
	Najran	76423	3.8%
Total		1988089	100%

4.5 Sample size

Different sample sizes were used in the relevant literature, usually depending on the scope of each study and the resources available to the researchers (Appendix 4). Typically, countries with established scientific evidence of medicine quality problems require a larger sample size from different locations. Moreover, studies with the aim of quantifying the prevalence rate of substandard or counterfeit medicines would require an increased number of samples with an appropriate sampling method. Nevertheless, studies reporting randomised sampling are scarce while the vast majority of published articles employ sample selection based on convenience (Newton et al., 2009).

The general warehouse in Riyadh is the primary point of receiving medicines from different manufacturers before they are distributed to all MOI primary care clinics in Saudi Arabia. For the purpose of this study, at least five different samples of each available batch number were collected from the MOI-MSD general warehouse in Riyadh. This will allow for any natural variation between different batches from the same manufacturer (Phanouvong & Blum, 2004). The WHO guidelines for sampling medicines states that collecting a single sample from a single batch would be adequate if they were from the same manufacturer, had the same batch number, had official documentation and were in sufficient quantities to conduct the required analytical tests (WHO, 2005). Furthermore, four additional glibenclamide samples from four different pharmaceutical manufacturers were conveniently collected from different community pharmacies in Najran for comparison purposes.

4.6 Materials and Methods

4.6.1 Chemical structure of glibenclamide

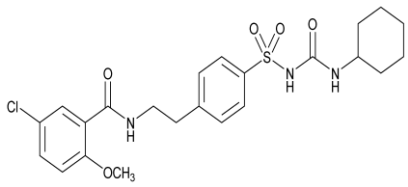


Figure 4.1 Chemical structure of glibenclamide

4.6.2 Glibenclamide sampling

To achieve these study objectives, a quantitative research approach using a cross-sectional survey method was adopted. Fifteen glibenclamide samples were collected overtly from the MOI-MSD general warehouse in Riyadh on one occasion only. Different brand names and batch numbers of glibenclamide available within the warehouse were identified electronically from available warehouse records and visually on site prior to data collection. Additionally, four different samples representing various batch numbers of four different glibenclamide manufacturers were conveniently obtained from community pharmacies in Najran in a two-month period between August and September 2014. The research collaborator was asked to covertly collect different samples from different community pharmacies in Najran. Four samples were collected from different community pharmacies that were selected at first sight from each area in Najran. Each community pharmacist was not aware of the purpose of the medicine purchase as the collaborator was instructed to ask to purchase the medicine for a relative without a prescription. None of the community pharmacists declined the purchase request. The covert collection of samples from community pharmacies using a mystery shopper technique was chosen based on similar studies widely available within the literature (Shakoor et al., 1997; Minzi et al., 2003; Atemnkeng et al., 2007; Bate et al., 2008; Tipke et al., 2008; Bate et al., 2009). Thus, a total number of 19 glibenclamide samples were available for analysis in this study.

Samples were collected from the MOI-MSD general warehouse on the 22nd August 2013 on a hot summer afternoon (12.30 pm) where temperatures were reported to reach 43 degrees Celsius. The researcher had previously contacted the MOI-MSD healthcare administration for this arrangement and agreed upon an appropriate time and date for the sample collection. Only one glibenclamide manufacturer was found in the warehouse with three different batch numbers available. Both electronic records as well as visual inspection confirmed this finding. The glibenclamide medicines were kept on fifteen different wooden pallets arranged in parallel positions. All the glibenclamide pallets were stored on the top shelves available in the warehouse. Hence, it was necessary for warehouse workers to assist the researcher with the collection of the required samples from the top shelves using a forklift truck (Appendix 5). This strategy

for sample collection was chosen to ensure the safety of the researcher in unfamiliar settings as well as minimising their selection bias. The warehouse workers were instructed by the researcher throughout the sampling procedure, except for the selection of the final medicine sample package from the medicine box row, where they were instructed to choose randomly at their preference. Each pallet contained 24 boxes while each box contained 144 sample units of medicines each containing 100 tablets/unit of package. Based on these calculations, the approximate number of glibenclamide sample units available for collection was 51,840 glibenclamide packages each containing 100 tablets of 5 mg glibenclamide concentration.

As previously mentioned, at least five different samples of each batch number were collected from the general MOI warehouse in Riyadh, in addition to the availability of at least 30 tablets/capsules in each sample to facilitate all necessary analysis tests similar to previous studies conducted by US pharmacopeia on medicine quality tests (Phanouvong & Blum, 2004). This allowed for any natural variation between different batches of the same manufacturer with a minimum number of sample size requirements and was in line with the WHO guidelines for medicine sampling (WHO, 2005).

A random strategy based on a systematic approach was employed to collect the samples from MOI warehouse. Pallets with different batch numbers (batches number 77, 89 and 90) were observed and recorded by the researcher. The objective was to collect five samples from each batch number for batch representation. When the batch number was represented by only one pallet (batch number 90), counting downwards each third row available in the pallet was selected for medicine box sampling. Also, counting from the left, each third medicine box was selected from the chosen pallet row. Each selected medicine box was then opened and the warehouse worker was instructed to select a medicine sample (package of 100 tablets) at his preference. Similarly, when batch numbers were represented by more than one pallet (batch number 77 had 3 pallets and batch number 89 had 11 pallets) a similar strategy was employed in addition to the selection of each third pallet counting from the left. When the count returned back to a previously chosen pallet and row, the third medicine box following our previously opened medicine box was chosen for sampling to include a wider representation of samples. The selected fifteen samples were then kept in plastic bags arranged in a box

where they were kept in room temperature and away from light for one week before being sent via a logistic company to the United Kingdom for analysis 60 days after collection. All sample documents were kept with the researcher at all times.

4.6.3 Glibenclamide chemical analysis

The chemical analysis for this study was performed using HPLC methods based on the findings from the systematic review (Chapter 3) and what the SFDA would routinely use to analyse medicines.

4.6.3.1 Duration and time

The chemical analysis process in this study started in November 2013 and the initial analysis was completed within three months for the samples collected from MOI-MSD general warehouse. The samples collected from Najran were analysed in a two-month period between September and October 2014.

4.6.3.2 HPLC analysis process

The HPLC analysis process for glibenclamide 5 mg (known as glyburide in the USA) was performed according to the latest United States Pharmacopoeial guidelines (USP 36) at the time of analysis (Appendix 6). Each sample was divided into 3 HPLC vials and run against reference sample in duplicate. The mean API% of each sample was then calculated according to the following equation:

Result = (rU/rS) × (CS/CU) × 100

rU = peak response from the sample solution

rS = peak response from the standard solution

CS = concentration of USP glyburide RS in the standard solution (mg/mL)

CU = nominal concentration of glyburide in the sample solution (mg/mL)

The acceptance criteria was 90-110% according to USP limits.

4.6.3.3 HPLC system

Shimadzu Autosampler SIL-20A/20AC

SIL-20AHT/20ACHT prominence High Performance Liquid Chromatograph

4.6.3.4 Chromatographic system

Mode: isocratic reversed phase LC

Detector: UV 254 nm

Column: 3.0×50 mm XTerra® RP18 3.5µ

Mobile phase: Ammonium dehydrate phosphate buffer (pH= 5.25)/acetonitrile (450:550 % v/v)

Flow rate: 0.25 mL/min

Sample run time: 15 min

Injection size: 10 µL

4.6.3.5 Preparation of mobile phase

Ammonium dihydrogen phosphate (2.6 g) was weighed and dissolved in 450 ml of deionised water. The solution was then transferred into a volumetric flask and shaking dissolved all powder. Then, 550 ml of acetonitrile was added to the solution, which was then filtered and degassed. The pH meter was used to measure the pH concentration prior to attachment to the HPLC system. The process was repeated twice throughout the experiment as required and on both occasions no pH adjustments were necessary as both readings fulfilled USP requirements of 5.25 ± 0.3 (5.29 and 5.46 respectively).

4.6.3.6 Preparation of reference sample (standard solution)

USP glyburide RS powder (10 mg, Sigma-Aldrich) was weighed and transferred into a 25 ml volumetric flask. Then, 20 ml of acetonitrile were added into the volumetric flask and shaken to dissolve. Subsequently, 4 ml of deionised water were added to the solution and then transferred to a HPLC vial for analysis following completing up to flask volume with a proportional mixture (25 ml Acetonitrile/5 ml deionised water).

4.6.3.7 Preparation of sample solution

Twenty tablets from each sample (equivalent to 100 mg glibenclamide) were crushed, weighed and transferred to a 250 ml volumetric flask. Then, 40 ml (equivalent to 0.4 mg/mL glibenclamide) of deionised water were added to the volumetric flask and the solution was swirled until complete dispersion. Subsequently, 200 ml (equivalent to 2 mg/mL glibenclamide) was added then the solution was shaken for 30 minutes. The sample solution was then centrifuged (8000 RPM for 10 minutes) and the clear supernatant was transferred to 3 coded HPLC vials for analysis following completing up to flask volume with a proportional mixture (100 ml Acetonitrile/20 ml deionised water). This process was repeated for each sample in this study.

4.6.3.8 Selection of 20 tablets to be analysed in each sample

Fifteen samples of glibenclamide 5 mg tablet (pack of 100 tablets) collected from MOI-MSD warehouse were all from a single manufacturer and with 3 different batch numbers. Each batch number was therefore represented by 5 packs. Each glibenclamide sample package contained 10 blister packs and each pack containing 10 tablets. It was possible to code each blister pack with a batch number and a blister pack number in order to select 2 random blister pack (20 tablets) from each sample. The randomisation was performed through a software www.randomizer.org to generate two random numbers for each batch (Appendix 7). This process was also performed for the other four samples collected from Najran community pharmacies for comparative purposes.

4.6.4 Glibenclamide visual analysis

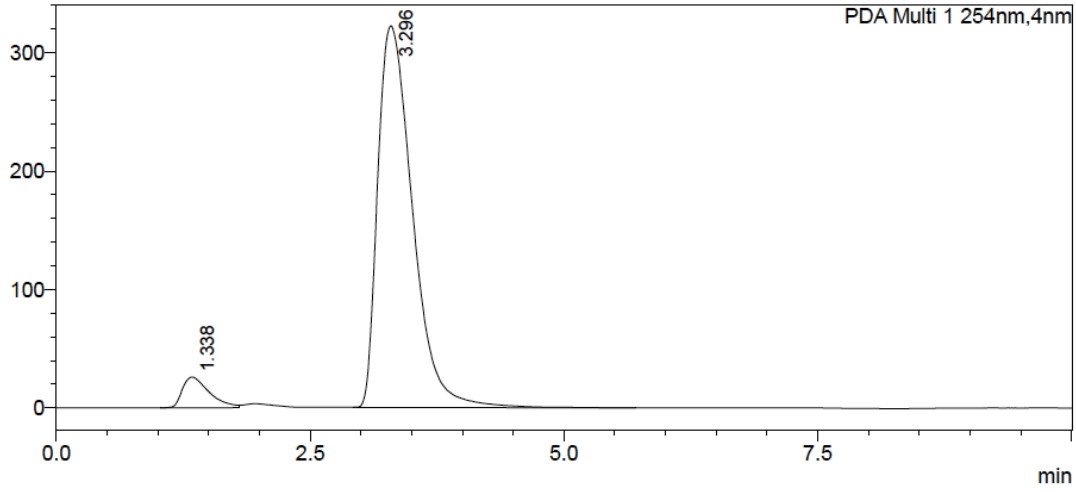
Visual inspection included medicine package checks for obvious errors and misspellings, missing package information (medicine name, dose, ingredients and manufacturer name and address) as well as the general appearance of medicine tablets. A draft data collection form adopted from two tool kits developed by The WHPA and FIP for visual inspection of medicines was utilised for this purpose (FIP, 2013). The tool included the sample code and name, package size, expiry date, collection date, package and tablet inspection, price, registration and results from the chemical test.

4.6.5 Glibenclamide authentication of source

Official records or communication with the manufacturer can determine the authentication of the source of each medicine sample. Since our study settings were mainly governmental primary care clinics, official medicine reception records were utilised to verify that each medicine sample has indeed been received from their manufacturers directly. Other authentication methods exist in the literature such as communicating with the manufacturer by telephone or e-mail, although the literature suggests that responses from companies cannot be always guaranteed (Khan et al., 2010; Nair et al., 2011). For the purpose of this study, official documents of reception have been collected and considered as sufficient evidence of product authenticity (Appendix 8). Hence, contact with the pharmaceutical manufacturers to verify the source of medicines was not necessary.

4.7 Results

The results of the chemical HPLC analysis of glibenclamide samples indicated the presence of the correct active pharmaceutical ingredient within the USP acceptance limits between 90-110% as shown in Table 4.3, when compared with the reference glibenclamide sample. An example of a sample and reference chromatograms can be found in Figures 4.2 and 4.3 respectively.

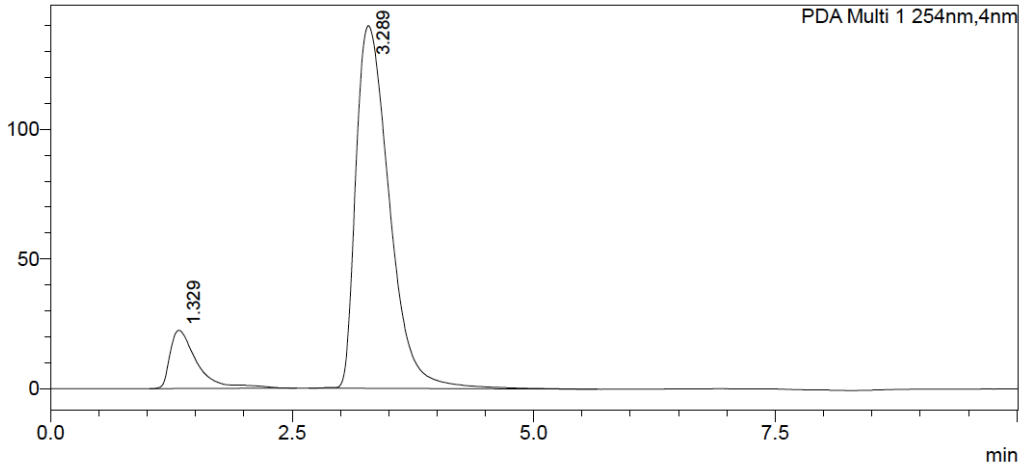


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	1.338	478110	25882	0.000			
2	3.296	7703800	322250	0.000			
Total		8181910	348132				

Figure 4.2 Example of glibenclamide batch 90 sample one first run chromatogram



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	1.329	436795	22380	0.000			
2	3.289	3377929	139812	0.000			
Total		3814725	162192				

Figure 4.3 Example of glibenclamide reference chromatogram

Table 4.3 Summary of API concentration found in glibenclamide samples

Sample name	Weight of 20 tablets (g)	Peak response from sample {Mean (SD)}	Peak response from standard {Mean (SD)}	Sample concentration (mg/mL)	Standard concentration (mg/mL)	API concentration (%)	Sample status
B77S1	3.1532	7555123 (23539.38)	3342591 (851.356)	0.9041	0.4000	100.00%	Accepted
B77S2	3.1713	7570157 (15436.64)	3342591 (851.356)	0.9059	0.4000	99.99%	Accepted
B77S3	3.1423	7431540 (63521.16)	3342591 (12822.6)	0.8893	0.4000	100.00%	Accepted
B77S4	3.2164	7544297 (31739.65)	3376532 (12822.6)	0.8937	0.4000	99.99%	Accepted
B77S5	3.2345	7636824 (74821.16)	3376532 (12822.6)	0.9046	0.4000	99.99%	Accepted
B89S1	3.2321	7802229 (30190.24)	3376532 (2174.35)	0.9180	0.4000	99.99%	Accepted
B89S2	3.2380	7695240 (14215.46)	3358398 (2174.35)	0.9165	0.4000	100.00%	Accepted
B89S3	3.2153	7730118 (13216.29)	3358398 (6827.82)	0.9206	0.4000	99.99%	Accepted
B89S4	3.2361	7783437 (7015.60)	3358398 (6827.82)	0.9270	0.4000	100.00%	Accepted
B89S5	3.2932	7953606 (10018.03)	4660425 (6827.82)	0.6826	0.4000	99.99%	Accepted
B90S1	3.2736	7871610 (18649.04)	4660425 (17134.6)	0.6756	0.4000	100.00%	Accepted
B90S2	3.2203	7729021 (9348.38)	4660425 (17134.6)	0.6633	0.4000	100.00%	Accepted
B90S3	3.3022	7793337 (5703.25)	4638998 (25065.5)	0.6719	0.4000	100.00%	Accepted
B90S4	3.2720	7903040 (1097.10)	4638998 (25065.5)	0.6814	0.4000	100.00%	Accepted
B90S5	3.2586	7914560 (6097.34)	4638998 (9157.03)	0.6824	0.4000	100.00%	Accepted
B3KT90	3.2122	7880760 (37668.13)	4695007 (6512.17)	0.6714	0.4000	99.99%	Accepted
B5872	3.8239	7690646 (81932.87)	4695007 (6512.17)	0.6552	0.4000	99.99%	Accepted
B71231	3.2380	8117232 (23138.97)	4657379 (32116.5)	0.7604	0.4000	91.67%	Accepted
BCT412	3.2807	7957436 (87868.17)	4657379 (32116.5)	0.7461	0.4000	91.59%	Accepted

An example of the calculation of the API concentration in samples is shown below:

USP Formula to calculate percentage of glyburide in samples:

Sample Area/Standard Area x Standard Concentration/Sample Concentration x 100

USP acceptance limit between 90-110%

Sample area: peak reading of API from the chromatogram
Standard area: peak reading of API from the chromatogram
Standard concentration: 10 mg of glyburide powder in 25 ml solution of water and acetonitrile that is equal to 0.4000 mg/ml
Sample concentration: calculated by the formula:
Sample Area/Standard Area x Standard Concentration

Example Batch 77 sample number one:
Sample area: 7546344
Standard area: 3342591
Standard concentration: 10 mg reference powder in 25 ml solution = 0.4000 mg/ml
Sample concentration: = Sample Area/Standard Area x Standard Concentration
= 7546344/3342591 x 0.4000 mg/ml
= 2.2576 x 0.4000 mg/ml
= 0.9030 mg/ml

Then by applying the USP acceptance formula:
Sample Area/Standard Area x Standard Concentration/Sample Concentration x 100
= 7546344/3342591 x 0.4000/0.9030 x 100
= 2.2576 x 0.4429 x 100
= 99.99% (accepted)

Furthermore, the visual analysis of glibenclamide medicine packages and the tablets did not reveal any unacceptable features, when examined according to the WHPA/FIP tool. Moreover, when the official documents of receiving glibenclamide batches delivered to the MOI-MSD were compared with the actual batches available at the MOI-MSD general warehouse, no discrepancies were found and were thus considered authentic and from the original manufacturing source.

4.8 Discussion

This study has identified the presence of the API in acceptable limits according to USP methods within glibenclamide medicine samples collected from MOI-MSD warehouse in Riyadh an community pharmacies in Najran in Saudi Arabia. Moreover, the visual analysis and authentication of source analysis were also performed and found to be acceptable in the MOI-MSD glibenclamide samples. These findings are reassuring, particularly with the growing evidence of global medicine problems, specifically with API quantity and identity as found in our systematic review of the literature (Chapter 3). Therefore, the subsequent parts of this study examined the perceptions of MOI-MSD stakeholders about medicine quality and their problem in order to explore the phenomena from a different and a social perspective.

Within the context of Saudi Arabia, this study was the first to examine glibenclamide API in Saudi Arabia. It did not identify any unacceptable quantities of API, as was found in previous studies that found such problems with amoxicillin in community pharmacies in Riyadh in Saudi Arabia (Kyriacos et al., 2008; Khoja et al., 2013a). This could be attributed to the different settings between these studies or the different API examined. Furthermore, these encouraging findings were similar to pharmacopoeial analysis studies that were performed in Saudi Arabia on other medications such as metformin (Afifi & Ahmadeen, 2012) that found them to contain the correct amount of API according to USP pharmacopoeial specifications.

There are several limitations that can be identified in this study. The cross-sectional survey design of the study would only permit relevance of the findings to a specific location and time. Further, glibenclamide was procured by the MOI-MSD healthcare services from a joint tender programme (GPP) which awards most medicines to different pharmaceutical companies each year, based on price competition. This would prove problematic if additional samples were required at a later time to confirm findings from this study.

The sample size in this study was determined based on similar small-scale studies conducted by the USP convention to analyse medicines in the absence of solid scientific evidence that would suggest a medicine quality problem at a particular location

(Phanouvong & Blum, 2004) and the WHO guidelines for sampling of pharmaceutical products (WHO, 2005). Examples of the sample size used in similar studies can be found in Appendix 4. Therefore, the findings from this study may not be generalisable. However, it can be suggested that a larger scale study over few procurement cycles could validate findings of this study.

Furthermore, the random strategy of sampling was mostly based on a systematic approach, where possible. However, for the final medicine selection from the medicine box, the warehouse worker performed the task, as it was not visible to the researcher from his standpoint. The time allowed for the medicine sample collection by the warehouse management would not permit for physical movement of pallets using a forklift truck to lower ground. Future medicine collection strategies could be performed in a systematic approach including the final medicine package selection particularly if present on lower shelves, where they can be visible to the principle researcher.

Moreover, some limitations are associated with the HPLC chemical analysis method used to test the API itself and not other medicine components such as excipients. The HPLC tests were performed to measure the API quantity only based on the findings from the previous study (Chapter 3) and previous studies in Saudi Arabia that have only found problems with API quantity (Kyriacos et al., 2008; Khoja et al., 2013a). It was not possible to conduct chemical identification tests, physical analysis tests or to confirm the authentication of source in samples collected from the community pharmacies in Najran since it was not one of the objectives of the study and could have compromised the covert collection of these samples by simulating everyday costumers in these settings.

The chromatograms obtained from the HPLC tests in this study (Figures 4.2 and 4.3) illustrated an unexpected peak in addition to the peak response from the sample and the reference chromatograms. It is possible that the second unexpected peak could be a result from degradation or deterioration of the samples used in the HPLC analysis. Existing literature supports this possibility as glibenclamide impurities such as related compound A (sulphonamide impurity) and related compound B (carbamate impurity) have been found in similar glibenclamide chromatograms (Sudha, Krishna & Kumar, 2014). Additionally, degradation may have also affected the two samples from Najran

(samples B71231 and BCT412) as they were found to contain a borderline API percentage content when compared with the USP acceptance criteria.

This phase of the study was considered a learning process for the principal researcher, as he is not a pharmaceutical analyst and his prior knowledge about such pharmaceutical analysis techniques was limited. Within this context, the laboratory examination of the samples in this phase of the study may have not been as rigorous as what is performed in the pharmaceutical industry. Additionally, system suitability tests were not performed in this phase of the study due to an oversight at the beginning of the analysis process and when it was addressed at later stages of the study, it was found to be associated with additional financial costs and therefore was not performed. However, although the system suitability tests were not performed, the resolution of the chromatograms was clear and the peaks obtained appeared to be sufficiently separated across all the results obtained from the chemical analysis. Moreover, only duplicate results were obtained from each sample and therefore the number of analysis replications may not be significant. However, the analysis of two samples from Najran were repeated with minimal differences in the results since they were found to contain less API than the other samples albeit within the accepted USP limits. It is possible that this finding could have been associated with unknown storage conditions of the samples collected from Najran as they were collected and sent to the UK by a research collaborator rather than the principal researcher.

4.9 Conclusion

Glibenclamide samples collected from MOI-MSD warehouse and community pharmacies in Najran in Saudi Arabia were found to be within acceptable USP API limits. The samples from MOI-MSD were found to be visually acceptable in terms of the medicine package itself and the tablets. Furthermore, it was possible to authenticate the source of the available glibenclamide samples at the MOI-MSD warehouse through cross-examination with the official consignment reception documents available. The finding of this study will be compared with other studies which explore the stakeholders' perception about medicine quality and related issues within MOI-MSD settings in the next phase of the study.

4.10 Ethical considerations

The medicine samples collected from all settings were coded and no brand/manufacturer name was revealed in the thesis in order to minimise the possibility of commercial use of the findings of this study. All official records and hardcopy data collected were in the possession of the researcher at all times or otherwise stored in a lockable storage area. With the possible exception of individual names appearing on official documents, no other people could be identified in this study. If medicine quality problems were detected after analysis, the MOI healthcare services would have been notified immediately of the findings of this study to protect patients from possible threats to their health. Since the medicine collection sites were mostly at a government setting, it was unlikely that the researcher would have been in any danger while collecting the samples. The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study (Appendix 9).

5 Chapter 5: A systematic review of perceptions about medicine quality and related problems

5.1 Introduction

Medicines with quality problems can be either counterfeit or substandard according to the World Health Organisation (WHO) classification (WHO, 2003a). A counterfeit medicine is charecterised by a deliberate and fraudulent mislabeling of the identity and/or source of the medicine itself or its packaging (WHO, 1999a). Substandard medicines, on the other hand, are legitimate medicines in terms of identity or source, but do not meet the required specification in terms of content and ingredients, as a result of poor manufacturing or storage conditions (WHO, 2003a; WHO, 2012a; Heyman & Williams, 2011; Yankus & Marks, 2009; Wertheimer & Norris, 2009; Clift, 2010). Collectively, both counterfeit and substandard medicines have been referred to as poor quality medicines by some researchers (Newton et al., 2010; Nayyar et al., 2012) and Substandard/Spurious/Falsely-labeled/falsified/counterfeit medicines (SSFFC) by the WHO (WHO, 2012a).

The threat from counterfeit and substandard medicines to society could be on different levels. More than 700,000 deaths from TB and malaria worldwide have been associated with ineffective treatment from counterfeit or substandard medicines (Cockburn et al., 2005; Mackey & Liang, 2011). Other examples of related fatal incidents include heparin contamination in the United States and adulterated life style drugs in Singapore (Kao et al, 2009; Luhn et al., 2011; Davison, 2011; Holzgrabe & Malet-Martino, 2011). Moreover, substandard and counterfeit medicines could lead to economic consequences such as loss of productivity, waste of limited resources and mitigating investments into pharmaceutical research and development (Moken, 2003; Yankus & Marks, 2009; Wertheimer & Norris, 2009). Furthermore, counterfeit and substandard medicines could lead to loss of confidence in healthcare organisations and their staff (Cockburn et al., 2005; Amin & Kokwaro, 2007; Wertheimer & Norris, 2009; Mackey & Liang, 2011; Kyriacos et al., 2008).

The true extent of the problem of counterfeit and substandard medicines remains largely unknown. However, the WHO estimates that around 10% of the global pharmaceutical supply is counterfeit and/or substandard: a figure that could reach up to 50% in developing countries and as low as 1% in the developed countries (Cockburn et al., 2005; Heyman & Williams, 2011; Ziance, 2008). Moreover, scientific research has addressed the problem of counterfeit and substandard medicines in the analysis of medicine samples collected from different countries. Detailed accounts of such studies can be found in systematic reviews elsewhere (Almuzaini, et al., 2013; Alghannam, et al., 2014).

The research into medicine quality and related problems has been largely focused on the actual quality of the medicine itself, demonstrated by laboratory testing (Patel et al., 2010). A detailed systematic review on non-laboratory research into counterfeit and substandard medicines is not available. The aim of this systematic review was to explore the existing scientific research on counterfeit and substandard medicines from a non-laboratory perspective. Specifically, the objective was to identify research articles addressing the views, perceptions and knowledge about counterfeit and substandard medicines from different stakeholders' perspectives. The results obtained from this systematic review helped the researcher in identifying the knowledge gaps in perspectives of stakeholders on counterfeit and substandard medicines and designing the next stage of the study.

5.2 Method

Scopus, PubMed, CINAHL Plus and MEDLINE databases were searched for relevant research articles. Our search covered all available periods up to 31st August 2015 and no language restrictions were applied. The following key search terms were used in conjunction with (AND) to identify related articles:

1- Substandard or counterfeit or "poor quality"
2- Medicine or drug or pharmaceutical
3- View or opinion or understanding or knowledge or experience or perception

This systematic review was performed in accordance with Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher et al., 2009). The inclusion criteria included articles that reported views, opinions or experiences of different stakeholders towards medicine quality and related problems such as counterfeit or substandard medicines from the selected databases and bibliography lists. In contrast, the exclusion criteria included articles investigating the actual quality of medicines through laboratory testing only, articles with no social contact with different stakeholders, duplicate and non-relevant articles. One reviewer (AFG) initially searched the selected databases and screened the titles/abstracts to exclude irrelevant and duplicate studies. Then, two reviewers (AFG and ZA) independently evaluated the remaining abstracts for possible inclusion. Any disagreement was resolved by discussion with the remaining authors (SE and FS).

The risk of bias in individual studies was addressed by performing a quality assessment on the selected studies. The quality of qualitative studies was assessed using Consolidated Criteria for reporting qualitative research (Tong, Sainsbury & Craig, 2007) with the addition of four criteria from the critical appraisal skills programme tool (CASP, 2013), namely having a clear aim, appropriate methods for the aim, ethical considerations and contribution to knowledge and future research as demonstrated in Table 5.1. The qualitative studies that scored between 0 to 12 were considered poor quality, between 13 to 24 were considered medium quality and studies that scored between 25 to 36 were considered high quality studies. Moreover, the quality of quantitative studies was assessed using a tool adapted from the STROBE statement (STROBE, 2007) with the addition of one criterion concerning ethical considerations as demonstrated in Table 5.2. The quantitative studies that scored between 0 to 10 were considered poor quality studies, between 11 to 20 were considered medium quality and studies that scored between 21 to 30 were considered high quality quantitative studies. Furthermore, the quality of mixed-method studies was assessed independently corresponding to their qualitative and quantitative components since there is a lack of an agreed, valid and reliable quality instrument in such mixed methods studies (O'Cathain, Murphy & Nicholl, 2008). The scoring system for the mixed methods studies was similar to the qualitative and quantitative studies scoring systems as previously described.

Table 5.1 Criteria for quantitative studies based on STROBE statement

Domain	Item number	Criterion
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract
	2	Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction	3	Explain the scientific background and rationale for the investigation being reported
	4	State specific objectives, including any prespecified hypotheses
Methods	5	Present key elements of study design early in the paper
	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
	7	Give the eligibility criteria, and the sources and methods of selection of participants
	8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.
	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
	10	Describe any efforts to address potential sources of bias
	11	Explain how the study size was arrived at
	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
	13	Describe all statistical methods, including those used to control for confounding
	14	Describe any methods used to examine subgroups and interactions
	15	Explain how missing data were addressed
	16	If applicable, describe analytical methods taking account of sampling strategy
	17	Describe any sensitivity analyses

Results	18	Report numbers of individuals at each stage of study
	19	Give reasons for non-participation at each stage
	20	Give characteristics of study participants
	21	Indicate number of participants with missing data for each variable of interest
	22	Report numbers of outcome events or summary measures
	23	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision
	24	Report other analyses done
Discussion	25	Summarise key results with reference to study objectives
	26	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
	27	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
	28	Discuss the generalisability (external validity) of the study results
Other Information	29	Give the source of funding and the role of the funders for the present study
	30	Discuss ethical approval of the study

Table 5.2 Criteria for qualitative studies based on Consolidated Criteria for Reporting Qualitative Studies and CASP tool

Domain	**Item number**	**Criterion**
Researcher's information	1	Specified who conducted the study
	2	Credentials
	3	Occupation
	4	Gender

	5	Experience and training
	6	Relationship with participants
	7	Participants' knowledge about the researcher
	8	Interviewer characteristics
Study design and data collection	9	Methodology orientation and theory described
	10	Sampling strategy described
	11	Approach described
	12	Sample size stated
	13	Non-participants described
	14	Clearly described data collection settings
	15	Presence of non-participants during data collection
	16	Description of sample
	17	Description of the interview guide
	18	Indicate if any interviews were repeated
	19	Describe type of recording of interviews
	20	Describe if field notes were used
	21	Indicate the duration of interviews
	22	Address data saturation
	23	Indicate if transcripts were returned to participants
Data analysis	24	Indicate who coded the data
	25	Description of the coding process
	26	Describe the derived themes
	27	Software used in the analysis where possible
	28	Participants' feedback on findings discussed
	29	Participants' quotes present in the themes

	30	Data and findings consistent
	31	Clear major themes
	32	Clear minor themes
Other Information	33	Clear aim for the study
	34	Appropriate methods for the aim
	35	Discuss ethical approval of the study
	36	Contribution to knowledge and future research

5.3 Results

5.3.1 Search results

The use of the selected search terms resulted in a total of 1,598 hits from all databases. An initial screening of titles/abstracts followed this, excluding non-relevant and duplicate results to reduce the number of hits to 120 research articles. Non-relevant articles included research conducted on quality of care, quality of life as well as research on non-pharmaceuticals. Subsequently, a full review of articles was performed, which further excluded studies that performed chemical analysis of samples only, review articles and opinion or letters where no primary data were collected. Furthermore, a manual search of bibliography lists was performed to include any relevant studies. This strategy reduced the final number of the included articles to sixteen. Figure 5.1 represents a flowchart illustrating the method used for article selection in this review.

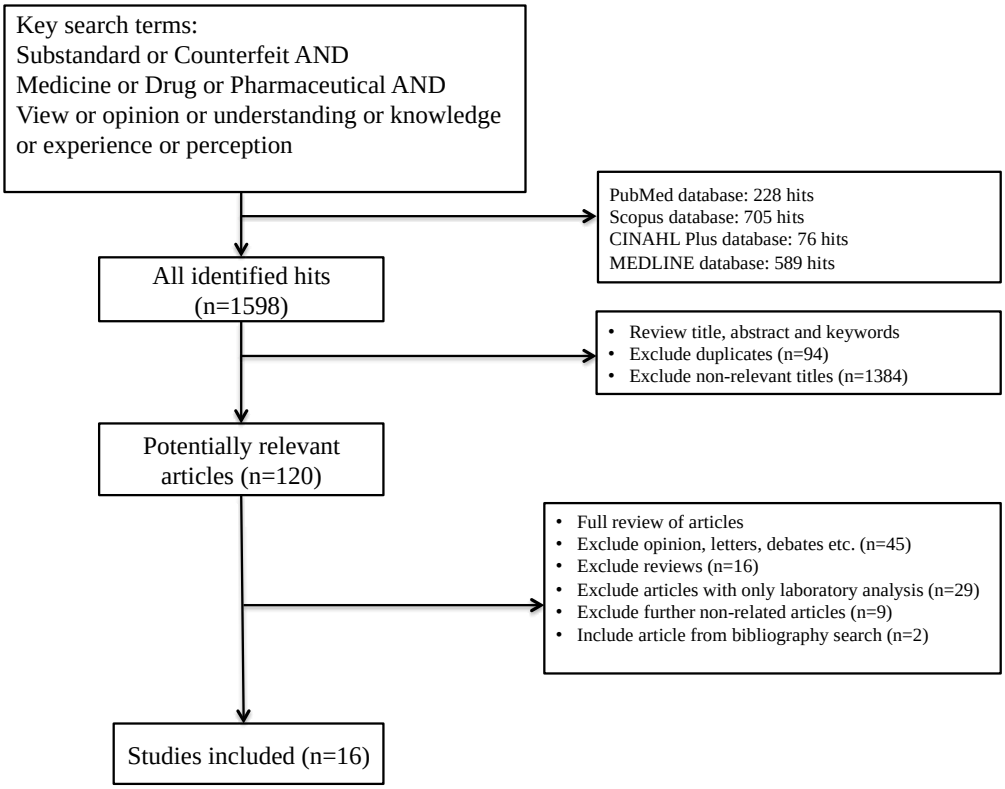


Figure 5.1 Flowchart for article inclusion in the second systematic review

5.3.2 Description of studies included

The search yielded a total of sixteen relevant articles. Seven studies (Dunne et al, 2014a; Dunne et al, 2014b; Lai & Chan, 2013; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Law & Youmans, 2011; Håkonsen & Toverud, 2011) were conducted in high-income countries according to the World Bank categorisation (The World Bank, 2015). Six studies (Shahverdi et al., 2012; García et al., 2011; Patel et al., 2010; Patel et al., 2009; Sharrad et al., 2011; Patel et al., 2012) were in upper-middle income countries. Two studies were identified (Alfadl et al., 2013; Syhakhang et al., 2004) in lower-middle income countries and one study (Khan et al., 2011) in a low-income country. Geographically, five studies (Dunne et al, 2014a; Dunne et al, 2014b; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Håkonsen & Toverud, 2011) were conducted in Europe. Five studies (Lai & Chan, 2013; Shahverdi et al., 2012; Sharrad et al., 2011; Syhakhang et al., 2004; Khan et al., 2011) were located in Asia. Four studies (Alfadl et al., 2013; Patel et al., 2010; Patel et al., 2009; Patel et al., 2012) were found in Africa. One study (Law & Youmans, 2011) was located in North America and one study (García et al., 2011) in South America.

Studies included in this review were found to have different aims. Seven studies (Lai & Chan, 2013; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Law & Youmans, 2011; Shahverdi et al., 2012; Alfadl et al., 2013; Khan et al., 2011) had counterfeit medicines as the aim of their research. Four studies (Patel et al., 2010; Patel et al., 2009; Patel et al., 2012; Syhakhang et al., 2004) were exploring medicine quality in general. Four studies (Dunne et al, 2014a; Dunne et al, 2014b; Håkonsen & Toverud, 2011; Sharrad et al., 2011) were assessing generic medicine perceptions. One study (García et al., 2011) investigated antimicrobial resistance and prescribing. In terms of stakeholders involved, ten studies (Dunne et al, 2014b; Lai & Chan, 2013; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Håkonsen & Toverud, 2011; Patel et al., 2010; Patel et al., 2009; Sharrad et al., 2011; Patel et al., 2012; Syhakhang et al., 2004) involved patients and/or medicine consumers. Five studies (Dunne et al, 2014a; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; García et al., 2011; Patel et al., 2012) were conducted with physicians. Five studies (Alfadl et al., 2013; Shahverdi et al., 2012; Law & Youmans, 2011; Syhakhang et al., 2004; Patel et al.,

2012) involved pharmacists and three studies (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Patel et al., 2012) involved nurses. Furthermore, some studies were conducted with other stakeholders such as a lawyer (Lai & Chan, 2013), health policy makers (Alfadl et al., 2013), a custom officer (Lai & Chan, 2013), pharmaceutical company representatives (Lai & Chan, 2013; Patel et al., 2009) and wholesalers and/or distributors (Khan et al., 2011; Patel et al., 2009).

5.3.3 Quality assessment results

Seven studies (Dunne et al, 2014a; Lai & Chan, 2013; Alfadl et al., 2013; Patel et al., 2009; Patel et al., 2010; Sharrad et al., 2011; Patel et al., 2012) included in this review had a qualitative design. Of these, the majority used semi-structured interviews (Dunne et al, 2014a; Lai & Chan, 2013; Alfadl et al., 2013; Patel et al., 2009; Sharrad et al., 2011; Patel et al., 2012) and some used focus group methods (Patel et al., 2010; Patel et al., 2012) to collect their data. The number of participants in these qualitative studies ranged from 5 to 73. Overall, the quality of the qualitative studies in this review was average. All qualitative studies were of medium quality with the exception of two high-quality studies (Patel et al., 2009; Patel et al., 2010). The main shortcomings were identified within the research team and reflexivity domain, where two studies (Dunne et al, 2014a; Lai & Chan, 2013) did not identify the person who conducted the interviews and only one study (Patel et al., 2009) described the researcher's experience and training in qualitative studies. For the research design domain, three studies (Lai & Chan, 2013; Patel et al., 2009; Patel et al., 2012) did not specify their methodological orientation and theory. All studies indicated the sampling procedure which was predominantly purposeful. Only three studies (Dunne et al, 2014a; Lai & Chan, 2013; Patel et al., 2009) disclosed information about non-participants and/or their reason for not taking part in the studies. The majority of qualitative studies clearly indicated the duration of data collection with the exception of two studies (Sharrad et al., 2011; Patel et al., 2012). Three studies (Dunne et al, 2014a; Alfadl et al., 2013; Sharrad et al., 2011) did not indicate whether the data transcripts/summaries were communicated back to the participants for comments and/or corrections. Only three studies (Dunne et al, 2014a; Alfadl et al., 2013; Sharrad et al., 2011) discussed data saturation in their studies. Moreover, within the analysis and findings domain, only two studies (Dunne et al,

2014a; Sharrad et al., 2011) clearly described the coding procedure and only one study (Patel et al., 2012) sought participant feedback on the study findings.

There were five studies (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Law & Youmans, 2011; Shahverdi et al., 2012; García et al., 2011) which adopted a quantitative cross-sectional design in this review. The quality of all these studies was found to be medium with only one high-quality study (García et al., 2011) excluded. The number of participants ranged from 155 to 1,455 in these studies. All studies indicated the study design and had a balanced summary of what had been done and found with the exception of one study (Law & Youmans, 2011). Similarly, all quantitative studies clearly described the participant eligibility criteria with one exception (Shahverdi et al., 2012). None of the studies discussed bias potential in their method section. Moreover, none of the studies explained how the sample size was calculated with only one exception (García et al., 2011). Missing data and participants' reasons for non-participation were not discussed in any of the included studies. All studies discussed the limitations, interpretation, generalisability and ethical considerations with one exception (Shahverdi et al., 2012).

Four studies (Dunne et al., 2014b; Håkonsen & Toverud, 2011; Syhakhang et al., 2004; Khan et al., 2011) were found to have a mixed-method design. However, only two studies (Dunne et al., 2014b; Syhakhang et al., 2004) clearly stated a mixed-method design for their study and only one study (Dunne et al., 2014b) justified the selection of a mixed-method design for their research. The quality of these mixed method studies was varied. Only one study (Syhakhang et al., 2004) had high quality in both the qualitative and quantitative components of the study. Another study (Dunne et al., 2014b) was found to be of medium quality in both the qualitative and quantitative parts. The remaining two studies were found to be of poor quality in the qualitative part (Håkonsen & Toverud, 2011; Khan et al., 2011) and ranged between medium quality (Håkonsen & Toverud) and high quality (Khan et al., 2011) in the quantitative part of the mixed method studies. Further details about these studies can be found in the Tables (5.3-5.5).

5.3.4 Knowledge about medicine quality

Several criteria have been found to define medicines with good quality according to different stakeholders' perceptions found in some studies. Having a good effect with minimal side effects was a key character of a good quality medicine according to patients in South Africa (Patel et al., 2010), patients and nurses in Lao PDR (Syhakhang et al., 2004) and both consumers and healthcare professionals in South Africa (Patel et al., 2012). Another reported perceived characteristic of a high quality medicine is that it should be a medicine that is expensive and from a well-known manufacturer, according to the opinion of urban customers and nurses in Lao PDR (Syhakhang et al., 2004). Additionally, medicine quality has been described in terms of the medicine itself and the manufacturing and handling processes involved with it in the opinion of different healthcare providers, pharmaceutical company representatives, wholesalers and distributers in South Africa (Patel et al., 2009). In contrast, the definition of counterfeit medicines has been reported in two studies (Alfadl et al. 2013; Khan et al., 2011). A counterfeit medicine has been described as a medicine entering the country from illegal channels and having different standards to the previously approved specifications, according to some healthcare commissioners in Sudan (Alfadl et al. 2013). Furthermore, managing executives of Cambodian wholesalers defined a counterfeit medicine as an unregistered product, fraudulently manufactured, containing less than stated active pharmaceutical ingredient, without batch or lot number, containing harmful substances and expired medicines (Khan et al., 2011).

The knowledge and awareness about the scale of counterfeit medicines has been found in some studies (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Shahverdi et al., 2012). One study found that the physicians and nurses in Poland had less awareness about the scale of counterfeit medicines and the threats they posed when compared to lay people (Binkowska-Bury et al., 2012a). A similar study found that lay people had slightly lower awareness about counterfeit medicines in comparison to physicians and nurses in Poland (Binkowska-Bury et al., 2012b). Pharmacists in Iran were also found to have low knowledge about counterfeit medicines (Shahverdi et al., 2012).

5.3.5 Perceptions about medicine quality

Two studies investigated the perception about medicine quality in general in South Africa (Patel et al., 2012) and Lao PDR (Syhakhang et al., 2004). All healthcare providers in the study conducted in South Africa thought that medicine quality was good in their country (Patel et al., 2012). Most nurses (80%) and customers (62%) held the belief that all medicines in Lao PDR were of a good quality (Syhakhang et al., 2004). However, there were some results that suggested a degree of confusion between medicine quality problems and other pharmaceutical issues. For instance, 12% of the GPs (Dunne et al., 2014a) and 24% of patients (Dunne et al., 2014b) in Ireland held the view that generic medicines were of poor quality. Some consumers in South Africa shared similar views that generic medicines are of inferior quality (Patel et al., 2010; Patel et al., 2012). In Peru, one study (García et al., 2011) found that 57% of physicians who participated in the study were of the opinion that the generic antibacterial medicines in their own settings were of poor quality. Medicines from China and India were also perceived as poor quality medicines by some healthcare providers in South Africa (Patel et al., 2012). Furthermore, some studies reported the perception that generic medicines are counterfeit or fake. In one study 25% of recruited Pakistani participants living in Norway thought that generic medicines were counterfeit (Håkonsen & Toverud, 2011). Another study (Patel et al., 2012) found that some customers in South Africa believed that cheaper generics were fake medicines.

5.3.6 Practice to ensure medicine quality

Few studies (Patel et al, 2009; Khan et al., 2011) discussed specific strategies to ensure medicine quality in their settings. Patel et al (2009) identified procurement from licensed suppliers, use of standard operating procedures and audits as key strategies to ensure medicine quality. More than 50% of medicine wholesalers in a Cambodian study (Khan et al., 2011) indicated that they would consider the local registration status, credibility of the product and reputation of the manufacturer during procurement. They would also consider intactness of medicines, their specification, local registration, batch and/or lot number and the name of the manufacturer during the reception of medicine consignments.

Barriers to practices to ensure medicine quality and associated challenges were also identified in some studies. Lack of communication with authorities regarding medicine quality problems and appropriate feedback were reported in two studies (Law & Youmans, 2011; Patel et al., 2009). Lack of resources and the use of online pharmacies were identified in one study (Law & Youmans, 2011). In another study, Shahverdi et al. (2012) found a low practice level in Iranian pharmacists towards counterfeit medicines, particularly in attending educational courses about them. Furthermore, two studies in Poland (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b) found that the majority of their responding physicians and nurses did not know the procedure to report suspicious medicines. However, Law & Youmans (2011) report that 52% of Californian pharmacists in the United States who responded to their questionnaire indicated that they would report encountering a counterfeit medicine to the FDA, board of pharmacy or their headquarters. Lenient penalties for medicine counterfeiters were also identified as a challenge to ensuring medicine quality (Lai & Chan, 2013).

Table 5.3 Characteristics of studies that used thematic analysis of data

Reference	Country	Sample	Study type	Method of analysis	Study purpose	Quality of study
Dunne et al. (2014a)	Ireland	34 General practitioners	Semi-structured interviews	Thematic analysis	Assess the perceptions regarding generic medicines	**
Lai & Chan (2013)	Hong Kong	5 individuals from a pharmaceutical company, patient, lawyer and a custom officer	Semi-structured interviews	Thematic analysis	Understand the anti-counterfeit legislation from a legal perspective	**
Alfadl et al. (2013)	Sudan	11 Health policy makers and community pharmacists	Semi-structured interviews.	Thematic content analysis	Seek insight into the determining factors of counterfeit medicine	**
Patel et al. (2010)	South Africa	73 public participants	12 Focus groups	Thematic analysis	Explore perception about drug quality and their influence on procurement	***
Patel et al. (2009)	South Africa	9 decision-making participants in South Africa from pharmaceutical industry and one dispensing doctor	Semi-structured interviews	Thematic analysis	Explore perception about drug quality and how the quality of drugs is ensured	***
Sharrad et al. (2011)	Iraq	14 consumers in Basra	Semi-structured interviews	Thematic content analysis	Explore perception and knowledge about generic medicines	**
Patel et al. (2012)	South Africa	73 consumers and 15 healthcare providers (doctors, nurses and pharmacists) from public and private sectors	Focus groups with consumers and semi-structured interviews with healthcare providers	Thematic analysis	Compare the consumers and healthcare providers perception of generic quality with the actual quality of some products	**

Table 5.4 Characteristics of studies that used monovariate and bivariate analysis of data

Reference	Country	Sample	Study type	Method of analysis	Study purpose	Quality of study
Binkowska-Bury et al. (2012a)	Poland	1,455 in total. 1,078 healthcare staff (268 physicians and 810 nurses) and 377 lay people	Cross-sectional survey Self-administered questionnaire	Bivariate analysis using Chi-Square test	Gain information on the difference in understanding of counterfeit medicines between healthcare professionals and lay people	**
Binkowska-Bury et al. (2012b)	Poland	651 in total. 102 physicians, 99 nurses and 450 lay people	Cross-sectional survey Self-administered questionnaire	Bivariate analysis using Chi-Square test	Gain information on the difference in understanding of counterfeit medicines between healthcare professionals and lay people	**
Shahverdi et al. (2012)	Iran	734 pharmacists attending a conference	Cross-sectional survey Self-administered questionnaire	Bivariate analysis	Assess knowledge and measure professional attitude and practice of pharmacists about counterfeit medicines	**
García et al. (2011)	Peru	256 medical doctors in 2 tertiary hospitals	Cross-sectional survey Self-administered questionnaire	Bivariate analysis using Chi-Square test or Fisher exact	Evaluate knowledge, attitude and practice about antimicrobial resistance and prescribing	***
Law & Youmans (2011)	USA	155 pharmacists in California	Cross-sectional survey Self-administered questionnaire via the web	Univariate analysis expressed by numbers and percentages	Examine knowledge of counterfeit medicines, impact of technology, barriers to involvement and potential roles to undertake	**
Khan et al. (2011)	Cambodia	62 managing executives of registered pharmaceutical wholesalers	Semi-structured questionnaire and observational section about storage conditions	Bivariate analysis for quantitative data using Fisher's exact test and Chi-Square test	Explore the knowledge of, perception on and practices related to counterfeit medicines	* For qualitative *** For quantitative

Table 5.5 Characteristics studies that used combination of thematic analysis and monovariate or bivariate analysis of data

Reference	Country	Sample	Study type	Method of analysis	Study purpose	Quality of study
Dunne et al. (2014b)	Ireland	42 patients	Semi-structured interviews and structured questions with a 5 point Likert scale system	Thematic analysis for qualitative data and Univariate analysis for quantitative data	Assess patient perception of generic medicines	** Qualitative and quantitative
Håkonsen & Toverud (2011)	Norway	83 Pakistani patients	Semi-structured interviews	Content analysis for qualitative data and Univariate analysis for quantitative data	Explore the perception towards generic substitution and how it would influence medicine adherence	* For qualitative ** For quantitative
Syhakhang et al. (2004)	Lao PDR	59 nurses and 278 customers	Structured interviews with drug sellers and exit customers. Focus group discussions with community members and drug sellers	Thematic analysis for qualitative data and Bivariate analysis for quantitative data	Explore knowledge and perceptions regarding drug quality in the chosen population	*** Qualitative and quantitative

Table 5.6 Unifying themes and contributing subthemes from stakeholders' papers

Theme	Subtheme	Reference
Definition of a good quality medicine	Registered by authorities	Patel et al. (2009) Syhakhang et al. (2004)
	Has good effect	Syhakhang et al. (2004) Patel et al. (2009) Patel et al. (2010) Patel et al. (2012)
	Has original colour	Syhakhang et al. (2004)
	Expensive medicines	Syhakhang et al. (2004)
Definition of a counterfeit medicine	A medicine from illegal source	Alfadl et al. (2013b) Khan et al. (2011)
	Has different standards to registered products	Alfadl et al. (2013b) Khan et al. (2011)
	Non-registered medicine	Khan et al. (2011)
	Expired medicines	Khan et al. (2011)
Strategies to ensure medicine quality	Procurement from licensed suppliers	Patel et al. (2009)
	Use of standard operating procedures	Patel et al. (2009)
	Audits between manufacturers and providers	Patel et al. (2009)
	Check medicine registration status	Khan et al. (2011)
	Consider manufacturer's reputation	Khan et al. (2011)
	Visual check of labeling information	Khan et al. (2011)
	Check analytical certificates	Khan et al. (2011)
Barriers and concerns to medicine quality	Communication and reporting	Patel et al. (2009) Patel et al. (2012) Binkowska-Bury et al. (2012a) Binkowska-Bury et al. (2012b) Law & Youmans (2011)
	Generic and free medicines perceived as inferior in quality	Patel et al. (2010) Patel et al. (2012) Dunne et al. (2014b) Dunne et al. (2014a) Garcia et al. (2011) Håkonsen & Toverud (2011) Sharrad et al. (2011) Syhakhang et al. (2004)
	Generic medicines perceived as counterfeit	Håkonsen & Toverud (2011) Patel et al. (2010)
	Developing countries perceived as manufacturing inferior quality medicines	Patel et al. (2012)
	Generic medicines perceived as less monitored than brand medicines	Patel et al. (2012)
	Lack of education about counterfeit medicines	Alfadl et al. (2013b) Shahverdi et al. (2012) Binkowska-Bury et al. (2012a) Binkowska-Bury et al. (2012b) Law & Youmans (2011)
	Penalties to counterfeiters are lenient	Lai & Chan (2013)

5.4 Discussion

Research articles were found from twelve different countries including South Africa (Patel et al., 2009; Patel et al., 2010; Patel et al., 2012), Poland (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b), Ireland (Dunne et al., 2014a; Dunne et al., 2014b), Hong Kong (Lai & Chan, 2013), Sudan (Alfadl et al., 2013), Iraq (Sharrad et al., 2011), Iran (Shahverdi et al., 2012), Peru (García et al., 2011), USA (Law & Youmans, 2011), Norway (Håkonsen & Toverud, 2011), Lao PDR (Syhakhang et al., 2004) and Cambodia (Khan et al., 2011). However, no studies were found in higher income countries in the western parts of Asia, Australia and South America. Similarly, no studies were found in European countries from the middle and low-income group. Evidence from Africa was only found in the middle-income group and no African studies were found in the high or low-income groups. Furthermore, the included studies were found to have different aims and objectives. The majority of included studies (Lai & Chan, 2013; Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b; Law & Youmans, 2011; Shahverdi et al., 2012; Alfadl et al., 2013; Khan et al., 2011) focused their research on counterfeit medicines. Some studies (Patel et al., 2010; Patel et al., 2009; Patel et al., 2012; Syhakhang et al., 2004) had a general explorative aim of the understanding of medicine quality. Interestingly, we found few articles with other aims and objectives such as perceptions of generic medicines (Dunne et al, 2014a; Dunne et al, 2014b; Håkonsen & Toverud, 2011; Sharrad et al., 2011) and one study (García et al., 2011) explored antimicrobial resistance and prescribing. This finding suggests that a degree of confusion between such subjects and medicine quality problems is possible from the perspective of different stakeholders. Furthermore, it was possible to arrange the outcomes from this systematic review into three categories concerned with knowledge and awareness of medicine quality and their problems, perceptions about medicine quality and practices to ensure medicine quality.

Knowledge about medicine quality appears to be limited when considered in terms of the number of cited studies in literature, exploring the issue and their results. It appears that medicine quality is commonly comprehended by its perceived effect for both patients (Patel et al., 2010; Patel et al., 2012) and healthcare professionals (Patel et al., 2009; Patel et al., 2012; Syhakhang et al., 2004). A high quality medicine was also

linked with having a higher price according to other findings (Syhakhang et al., 2004; Alfadl et al., 2013). However, it is widely accepted that a high quality medicine should be defined according to its fulfillment of pharmacopoeial specifications (Quick et al., 1997; Patel et al., 2009). This view can also be extended to include all related activities and services that could affect the quality of medicines (WHO, 2004). Examples of such criteria include: that the medicine is registered with healthcare regulators and has a correct label that clearly identifies the name of the medicine, the strength, lot number, expiry date, instructions for use and the manufacturer's address (WHO, 1997; Syhakhang et al., 2004).

Counterfeit medicines have also been described as medicines without registration and entering the market illegally (Alfadl et al., 2013; Khan et al., 2011). Other descriptors of counterfeit medicines found include fraudulent manufacturing, having less than stated active pharmaceutical ingredient, containing harmful substances and missing some packaging details (Khan et al., 2011). These views closely resemble the WHO definition of counterfeit medicines which highlights issues of packaging and product identity and/or source (WHO, 1999). However, both studies (Alfadl et al., 2013; Khan et al., 2011) were conducted with healthcare commissioners and wholesaler executives. No study was found that explored the understanding of counterfeit medicines within healthcare professional staff and the members of the community.

Evidence from some of the cited studies suggests a possible confusion between generic medicines and poor quality medicines, or even counterfeits. Some healthcare professionals, physicians in particular, have been reported to have a perception that generic medicines are of poor quality (Dunne et al., 2014a; García et al., 2011; Patel et al., 2012). Patients could also share some of these views of the inferior quality of generic medicines according to some studies (Dunne et al., 2014b; Patel et al., 2010). Furthermore, it has been reported that some patients could have the perception that generic medicines are counterfeit or fake (Håkonsen & Toverud, 2011; Patel et al., 2012). Such perceptions could have a negative impact on generic medicine prescription and use for all different stakeholders. Therefore, it is imperative to extend the research into understanding the perceptions about medicine quality problems to gain more insight about the scale of confusion between generic medicines and poor quality or

counterfeit medicines in various contexts. Furthermore, it is possible to use public health campaigns as a means of educating the healthcare professionals and public about medicine quality and their problems in order to minimise the magnitude and effect of such confusion (Po, 2001; Syhakhang, 2004).

There were a limited number of cited articles that addressed specific practices implemented to ensure medicine quality. Practices in the medicine procurement phase were found to emphasise the reliability of source and the registration status of the medicines as key strategies to ensure the quality of a medicine (Patel et al., 2009; Khan et al., 2011). Other considerations during medicine procurement included the use of standard operating procedures and audits (Patel et al., 2009). The practices during the reception of medicine consignments focused on the investigation of the medicine package in terms of appearance and the information included (Khan et al., 2011). It has been established that medicine quality should be ensured throughout the medicine cycle starting from manufacturing, procurement, storage and distribution (WHO, 2007). However, none of the cited articles explored the practices during the manufacturing, storage and distribution phases of the medicine cycle. It could be interesting to explore such reports about practices in future research and compare it with the actual practice in an observational study.

This systematic review has several strengths. To the researcher's knowledge, this was the first systematic review examining the stakeholders' perception about medicine quality and related problems such as counterfeit and substandard medicines. A comprehensive literature search, use of stringent inclusion and exclusion criteria, and the use of recognised methods from the literature to assess the quality of included studies was followed to locate relevant studies and extract the necessary data. The extracted information from this systematic review could be beneficial in raising the awareness of healthcare authorities, industries and interested researchers about the perception of medicine quality and related problems such as counterfeit and substandard medicines in order to design appropriate strategies to enhance medicine safety, accessibility and use.

Findings from this systematic review should not be interpreted without considering its limitations. The systematic review nature of this study would only allow for observation of trends rather than their causes from the available data. There was a diverse range of study designs in the included studies that could introduce the possibility of bias. The search process was limited by the search strategy used in this review in terms of the selected databases, keywords, and inclusion and exclusion criteria. This review was limited to the available data found in studies from only twelve countries, which could limit the generalisability of findings. However, the limited number of identified studies would suggest that further research is needed on the subject. Furthermore, it was found that there was some degree of integration between the perceptions of medicine quality problems with the perception of generic medicines in some of the studies included. However, the aim was to focus the search on perceptions of medicine quality and their problems and, therefore, the findings do not claim to include all perceptions regarding generic medicines particularly the bibliographic lists from the relevant research articles. Furthermore, there was a degree of difficulty in the quality assessment of studies using a mixed-method design. It has been suggested that there is an absence of an agreed, valid and reliable measure for the quality assessment of mixed methods studies (O'Cathain et al., 2008; Twyman, Bonevski, Paul & Bryant, 2014). Hence, recognised methods to evaluate the quantitative and qualitative components independently for each included mixed methods study was used in an attempt to evaluate their quality overall.

5.5 Conclusion

Evidence about perceptions, practices and knowledge of medicine quality and their problems remains limited. The quality of the available research articles was mostly moderate. A high quality medicine was commonly defined in terms of perceived effect by healthcare professionals and patients. Other reported criteria of a high quality medicine included expensive price, manufacturing and handling of the medicine itself. Counterfeit medicines were defined as medicines from illegal sources, non-registered and with inaccurate product specifications. Some confusion was found between the issues of generic medicines and poor quality medicines including counterfeits. The reported practices to ensure medicine quality focused on the procurement and the reception of consignment phases. Further in-depth research into the subject of perceptions, practices and knowledge of medicine quality and their problems is required in order to gain further insight into the phenomenon and their prevalence in different contexts. Such insights could be helpful in identifying gaps in knowledge about the issue and help in designing appropriate strategies to increase the stakeholders' knowledge and awareness about medicine quality problems and to minimise confusion with other issues such as generic or cheaper medications that could affect their availability and use.

6 Chapter 6: Stakeholders' perception about medicine quality and related issues in the MOI-MSD in Saudi Arabia

This chapter consists of five phases. Phase 1 explores the scope of stakeholders' perceptions and developing questions about medicine quality and related problems for subsequent phases of the study through conducting a focus group. Phase 2 explores the MOI-MSD commissioners' perceptions about medicine quality and related problems through interviews. Phase three examines the MOI-MSD patients' perceptions about these issues by interviews. Phases 4 and 5 explores the MOI-MSD pharmacists' and physicians' perceptions about these issue by a questionnaire survey and interviews. A flowchart (Figure 6.1) illustrates an overall view of this chapter.

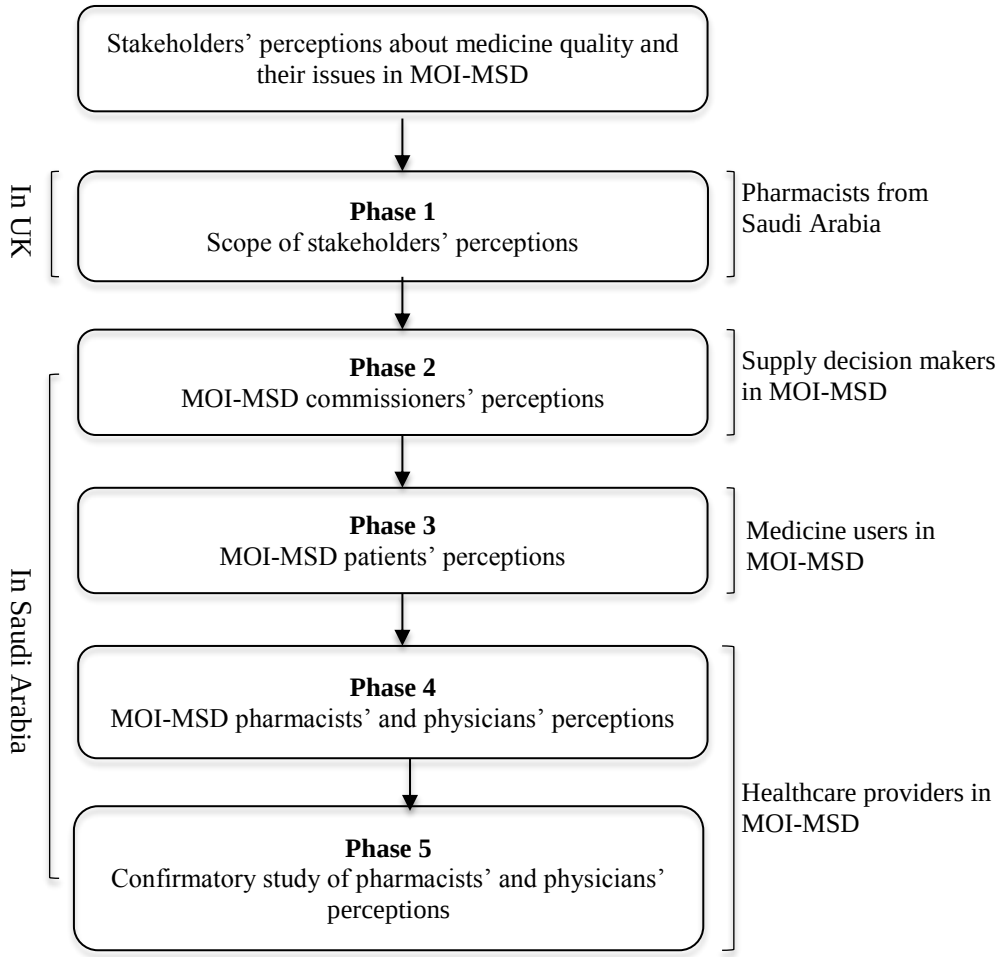


Figure 6.1 Flowchart illustrating phases of stakeholders' perception about medicine quality and their problems study in MOI-MSD in Saudi Arabia

6.1 Introduction to stakeholders' perceptions about medicine quality

Medicine quality problems can either be counterfeit or substandard according to the WHO (WHO, 2003a). A counterfeit medicine is defined as a medicine that is deliberately and fraudulently mislabeled in terms of identity and/or source according to the WHO definition (WHO, 1999a). Substandard medicine can be defined as a legitimate medicine from a legitimate source that demonstrates a degree of unacceptable standards when compared with the required specifications (WHO, 2003a; WHO, 2014). Both types of medicine quality problems could lead to undesired effects on the public health, the economy and damage trust between healthcare providers and beneficiaries. For example, more than 700,000 deaths from TB and Malaria around the world were strongly associated with poor quality medicines (Cockburn et al., 2005; Mackey & Liang, 2011). Counterfeit and substandard medicines were also responsible for several reported deaths in the USA and Singapore (Kao et al, 2009; Luhn et al., 2011; Davison, 2011; Holzgrabe & Malet-Martino, 2011). Economically, counterfeit and substandard medicine could result in wasting limited resources and causing unnecessary financial burdens associated with inadequate treatment and patient hospitalisations (Yankus & Marks, 2009; Wertheimer & Norris, 2009). Furthermore, counterfeit and substandard medicines may cause loss of faith and trust in healthcare providers in a degree that exceeds the medicines themselves to include other healthcare practices (Cockburn et al., 2005; Amin & Kokwaro, 2007; Wertheimer & Norris, 2009; Mackey & Liang, 2011; Kyriacos et al., 2008).

Traditionally, the quality of medicines has been established through laboratory testing of medicine samples in comparison with various pharmacopoeial requirements (Patel et al., 2010). The findings from a systematic review conducted previously (Chapter 5) suggested that limited research has been conducted to understand medicine quality and their problems from the perspectives of different stakeholders and in non-laboratory settings.

6.2 Overall aim of stakeholders' perception study

The overall aim of this chapter was to explore the commissioners', healthcare providers' and patients' perspectives on medicine quality and related issues such as counterfeit and substandard medicines in the MOI-MSD in Saudi Arabia.

6.3 Objectives of stakeholders' perception study

The specific objectives of this study included the following:

- Establishing stakeholders' beliefs and views about medicine quality and their problems.
- Explore the stakeholders' knowledge and behaviour about medicine quality and any related problems.
- Investigate potential improvements to the existing policies and procedures to address the issue of medicine quality problems in Saudi Arabia within the context of the global market.

6.4 Methods used in stakeholders' perception study

A mixed-method approach was adopted in this study. Triangulation by the use of different techniques for data collection and analysis to examine a single research problem was implemented in different phases in this study (Strauss & Corbin, 1990). Qualitative interviews helped to achieve an in-depth exploration of answers to the research questions from the perspective of healthcare professionals and patients. Quantitative survey questionnaires were useful in the estimation of the extent of such beliefs, views, knowledge and behaviour among healthcare professionals in MOI-MSD. Collectively, the use of both qualitative interviews and quantitative survey questionnaires increased the understanding of the patients' and healthcare professionals' perceptions about medicine quality and their problems in the MOI-MSD in Saudi Arabia. The sampling techniques used in this study included convenience sampling in the Saudi Arabian pharmacists' focus group and healthcare providers' interview phases, purposeful sampling in the commissioners' interview phase and random sampling in the health care providers' survey questionnaire phase.

The qualitative data analysis was based on thematic approaches in this study. In the focus group phase, themes were generated using a method adopted from Krueger &

Casey's (2009) steps for focus group data analysis. It involved data transcription, familiarisation and arrangement of participants' quotes in a specific order based on pre-determined questions to categorise data into themes. The analysis of interview data in this study was based on Strauss & Corbin's (1990) steps for interview data analysis. This approach involved data transcription, translation, familiarisation, assignment of initial codes, establishing connections between the codes and identifying themes and sub-themes after cross-examination of codes across all interviews.

6.5 Ethical approval for stakeholders' perception study

The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study (Appendix 9). The MOI-MSD has also issued similar letters of permission to conduct this study with their staff and patients (Appendices 10 and 11). All participants in this study were provided with participant information sheet to explain the purpose of the study and their confidentiality and/or anonymity rights, where applicable, prior to their recruitment (Appendices 12, 13 and 14). Furthermore, participants were reminded of their right to withdraw from the study at any time without the necessity to provide any explanation. All participants in the focus group and subsequent interview phases of the study were provided with consent forms (Appendices 15 and 16) entailing the previously mentioned conditions in order to obtain their signature for agreement to participate in this study prior to the start of the data collection process at each phase.

6.6 Phase 1: Scope of stakeholders' perceptions about medicine quality and their problems in Saudi Arabia

6.6.1 Introduction

Based on the findings from a previous systematic review (Chapter 5), limited research has addressed the issue of medicine quality and their problems from the perspectives of different stakeholders worldwide. It has also been found that some studies have addressed the issue of perspectives about medicine quality in general while other studies have focused on the perspectives about counterfeit medicines problem. However, none of the studies examined the perspectives of stakeholders about medicine quality in general and medicine quality problems such as counterfeit medicines concurrently. Furthermore, no studies were identified that explored the perspectives of any stakeholders about medicine quality and their problems in Saudi Arabia.

6.6.2 Aim

The overall aim of this study was to explore the scope of stakeholders' perceptions on medicine quality and related issues such as counterfeit and substandard medicines in Saudi Arabia in order to inform subsequent survey questionnaire and interview studies.

6.6.3 Objectives

The specific objectives of this study included the following:

- Establish pharmacists' beliefs and views about medicine quality and their problems.
- Explore their knowledge and behaviour about medicine quality and any related problems.
- Seek pharmacists' views on potential improvements that can be made to the existing policies and procedures to address the issue of counterfeit and substandard medicines in Saudi Arabia within the context of the global market.
- Identify Arabic words used to describe counterfeit and substandard medicines.
- The addition and deletion of questions for the survey questionnaire and interview studies to be used in the next phases of the study.

6.6.4 Methods

6.6.4.1 Recruitment of participants

The initial sample frame for this phase of the study consisted of twelve qualified Saudi Arabian pharmacists conducting postgraduate MSc and PhD studies during the academic year 2013/2014 at the University of Hertfordshire. No more than twelve invitations in total were sent for participant recruitment to address the possibility of attendance of all invited participants in this single group discussion and also the possibility of a low response rate. As a prerequisite for student acceptance on the MSc programme, candidates were required to have a minimum of one-year's practical experience. Similar requirements of practical experience were also obligated by Saudi Arabian governmental employers before sponsoring their staff to pursue postgraduate studies. However, it should be highlighted that the sampling approach in this phase of the study was based on convenience and therefore could be bias towards the opinions of the participants who agreed to participate in this phase of the study.

6.6.4.2 Question design and order

The questions for this phase of the study were exclusively open-ended and were developed following the systematic review (Chapter 5) and a specific literature research of interview guides and questionnaire samples found in relevant articles (Syhakhang et al., 2004; Patel et al., 2009; Khan et al., 2011; Law & Youmans, 2011; Alfadl et al., 2012; Patel et al., 2012; Binkowska-Bury et al., 2012a; Shahverdi et al., 2012) with the addition of some questions to address the aim and objectives of this phase of the study. Two academic members of staff at the University of Hertfordshire tested the questions for face validity. Appendix (17) contains the focus group schedule that includes the questions used for this phase of the study and Appendix (18) includes the demographic information sheet collected from the participants.

6.6.4.3 Data collection and study setting

A single focus group session was conducted in English in December 2013 and was completed within 93 minutes. Demographic and consent forms were completed by participants before the group discussion started. The group discussion was conducted within the Pharmacy Department at the University of Hertfordshire. This specific location was selected based on it is familiarity and accessibility to all participants. In

addition, the selected meeting room was equipped with video/audio recording equipment to facilitate data collection. The round table discussion was conducted with the use of a projector and a flipchart where the assistant moderator, also the supervisor of this study, recorded key points. The group meeting started with the research team introduction, appreciation of attendance and participants' round of introduction. Questions were asked to facilitate the group discussion regarding the topic of this research (Appendix 17). Then, the researcher delivered a short presentation to the participants in order to describe the phenomena of counterfeit and substandard medicines, as well as to outline the aim and objectives of the overall research study at the end of the meeting. This was followed by two questions asking the participants to translate the words "counterfeit" and "substandard" into Arabic. The meeting was then concluded with the appreciation for participants' involvement in this study.

6.6.4.4 Data analysis

A systematic strategy based on Krueger & Casey's (2009) steps to analyse focus group studies was adopted. The researcher transcribed the entire focus group session verbatim, then watched the videotape of the session while reading the written transcript for assertion and familiarisation with data. Multiple Microsoft Word documents were created to keep the original transcription, including a cut and paste document and an analysis document where similar quotes were collected together. Each quote was arranged in a suitable category, based on a specific decision-making process, by answering some questions. Subsequently, a summary of answers to each question was made without any interpretation at this stage. A scan of the summary of answers was followed to identify emerging themes to be used to report the findings regardless of the questions initial order. The data was left for a couple of days and then revisited in order to obtain an insight into the bigger picture of the findings and to conclude the analysis. The written report was then completed by adding no more than three quotes per theme as evidence of what had been said in the focus group session. The addition of the researcher's interpretation to the findings of the study was added at this stage and comparison of data made with the available literature to conclude the data analysis. Figure 6.2 illustrates the process of data analysis in this phase of the study.

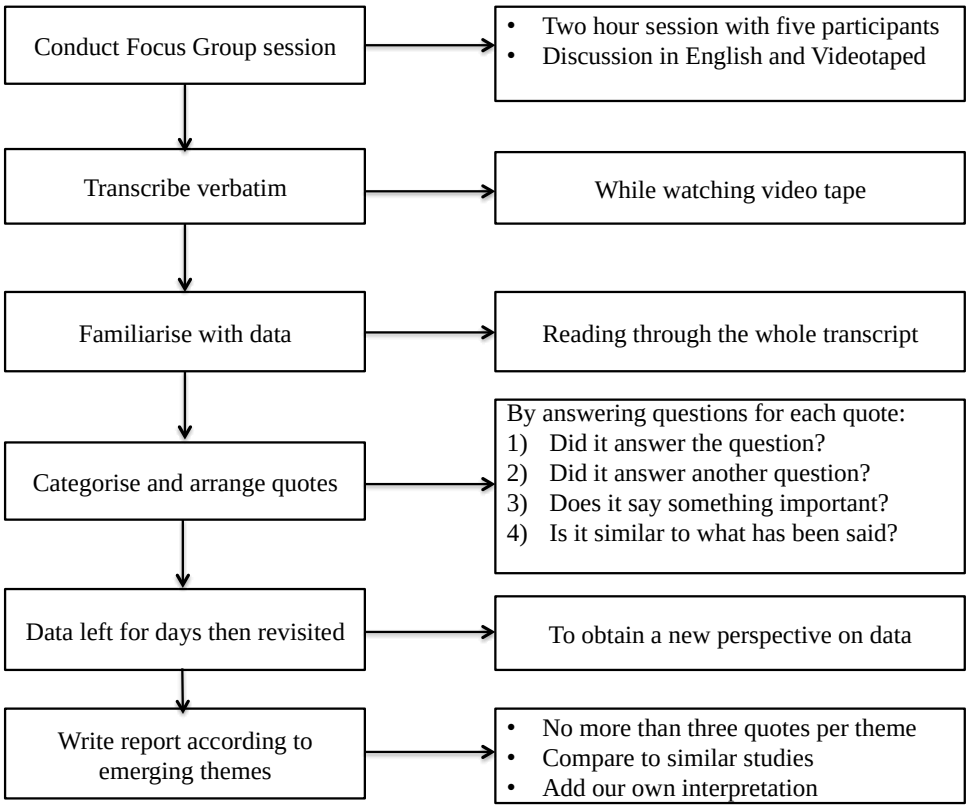


Figure 6.2 Strategy for data analysis for the scope of stakeholders' perceptions about medicine quality and problems in Saudi Arabia adopted from Krueger and Casey (2009)

6.6.5 Results

6.6.5.1 Participants' characteristics

Five participants attended the focus group discussion phase of this study. The overall response rate was 42.6 % (5 participants from 12 invited individuals). The participants were all Saudi Arabian pharmacists and included three male and two female participants. One participant was between the age of 26 to 30 while the remaining four participants were between the age of 31 and 35. Two participants had between 1 and 4 years of practical experience while the remaining three participants had between 5 and 10 years of work experience. The participants in this phase of the study worked in different regions in Saudi Arabia including the Central region (n=3), Northern region (n=1) and Southern region (n=1). Furthermore, the participants had worked in various governmental ministries in Saudi Arabia including the Ministry of Health (n=3) and other ministries (n=2). Further details about the participants' characteristics in this phase of the study can be found in Table 6.1.

Table 6.1 Focus group participants' demographic table

Participant code	Gender	Age (years)	Education	Governmental Ministry	Region of practice	Work experience (years)
Participant 1	Male	31-35	MSc	Ministry of Health	Central region	5-10
Participant 2	Male	31-35	MSc	Ministry of Health	Southern region	1-4
Participant 3	Male	31-35	BSc	Ministry of Defense	Northern region	5-10
Participant 4	Female	31-35	BSc	Ministry of Health	Central region	5-10
Participant 5	Female	26-30	BSc	Ministry of Defense	Central region	1-4

6.6.5.2 Themes

Eight themes emerged from the focus group discussion as follows:

Theme one: Definition of a good quality medicine

Most participants (4/5) indicated that a good quality medicine is a medicine that should have a good effect, where it would have a rapid effect with a minimum of side effects.

"I think for me it is the effect. If I was the patient and the effect of the medicine was okay, then that is a good quality medicine." (Participant 2)

Some participants (3/5) indicated that a good quality medicine should be available in different formulations and doses, to facilitate different requirements for different

patients. Others (2/5) believed that a good quality medicine should be affordable and have a good appearance in an attractive package. There were other individual (1/5) characteristics of a good quality medicine according to the participants, such as being previously used and accepted by the patient, present in a well regulated market and originating from a reliable source.

Theme two: Perceptions about medicine quality in Saudi Arabia

The majority of participants (4/5) believed that the quality of medicines in Saudi Arabia is high, that developed countries produce high quality medicine and that patients prefer brand name medicine manufactured in developed countries.

"Most people in Saudi Arabia think that medicines that come from developed countries like America or Europe has good quality more than medicines from Arab countries…" (Participant 4)

Some participants (2/5) indicated that physicians may share some of these negative views about the quality of generic medicines and advise their patients to procure brand medicines. There was one answer (1/5) where a participant indicated that some patients complained about some medicines not containing the active ingredient or with less than stated quantity of the active ingredient.

"Many patients complained about the active ingredient it not the same quantity as the British brand… they keep saying they don't have any active ingredient it is just powder you give us…it has less active ingredient" (Participant 5)

Theme three: Challenges to medicine quality in Saudi Arabia

The participants in the focus group discussion identified several challenges to the quality of medicines in Saudi Arabia on individual bases (1/5). There was no agreement among participants to each challenge identified in this theme. Examples of challenges to medicine quality in Saudi Arabia included poor storage conditions, extreme weather conditions, poor transport conditions, the presence of a single laboratory for medicine

clearance in the country and that hospitals from different organisations use different procurement practices to acquire their medicines.

"Sometimes I worry about how do you store it because sometimes in the summer it gets very warm" (Participant 1)

Theme four: Experiences with questionable quality medicines

Some participants (2/5) shared their experiences with medicine quality defects that were visually noticed.

"I also remember one IV injection … there was rubber inside…" (Participant 5)

There was one answer (1/5) where one participant recalled a previous encounter with counterfeit medicines while working in Hajj (Muslim pilgrimage season).

"I worked in the Hajj season…there is a lot of samples that are copied like the brand name but is different from the brand name when you compare the two boxes" (Participant 1)

Theme five: Price and quality relationship in medicines

All participants (5/5) in this phase study agreed that there was a relationship between price and quality of medicines. Some (2/5) indicated that expensive medicines had higher quality than cheaper alternatives.

"As a general impression with all the products not just medicines, you associate good quality with high price" (Participant 2)

There was one participant (1/5) who did not agree with the opinion that higher prices would always guarantee a high quality medicine.

"The government supports local manufacturers and for that reason the price of local products is cheaper than from other countries" (Participant 1)

Theme six: Assurance of medicine quality

Some participants (2/5) indicated that they check medicine expiry dates and storage conditions to ensure medicine quality. Other practices were reported on individual bases (1/5) such as dispensing medicines with ice bags if needed, visual check of medicine containers and on some occasions communicating with the regulatory authority laboratory to ensure that specific medicines were analysed and cleared for distribution.

"We check the temperature of medicines, we check for any crystals or particles or precipitation checked by more than one person" (Participant 4)

Theme seven: Knowledge about causes and impact of medicine quality problems

There was a clear understanding among all participants (5/5) in this study regarding the possible causes of medicine quality problems and their potential impact on health, economy and on trust between healthcare providers and patients.

"The other thing that it could break the trust of the patient, if that happens once to a patient, he will never trust anything again from this hospital" (Participant 2)

Theme eight: Recommendations to improve medicine quality in Saudi Arabia

Some participants (2/5) suggested that laboratory analysis of medicine samples would be helpful in order to improve the quality of medicines in Saudi Arabia.

"Select random samples to test in the lab…especially if that is the first time, also if some cases or reports coming it should be sent to the lab for testing" (Participant 1)

Other individual recommendations (1/5) included the improvement of the national reporting system for medicine quality problems, conducting more research on the topic, establishing appropriate punishments for individuals responsible for poor quality medicines, the rapid resolution of any poor quality medicine incident, the assessment of

the current registration process in the healthcare regulatory authority and for manufacturers to establish good practices and monitor the quality of their medicines.

6.6.5.3 Translation of counterfeit and substandard medicines into Arabic

All participants (5/5) in this phase of the study agreed that the term "maghshoosh" in Arabic was the most appropriate translation of the term counterfeit. However, none of the participants was able to translate the term substandard medicines into Arabic.

6.6.6 Discussion

The majority of participants in this focus group study defined a good quality medicine in terms of its perceived effect on the patient. This result is in line with other findings from the perspective of nurses in Laos (Syhakhang et al., 2004), healthcare professionals in South Africa (Patel et al., 2009; Patel et al., 2012) and patients in South Africa (Patel et al., 2010; Patel et al., 2012). However, such a definition of a good quality medicine does not take into account that a medicine may not generate the desired effect for other reasons besides its quality, such as incorrect diagnosis, wrong selection of medicine or dosage form, medicine non-adherence or medication errors (Quick et al., 1997; Patel et al., 2009). Therefore, it becomes imperative that healthcare professionals in particular and the public in general become aware of the possibility of such treatment failures, in order to avoid confusion between medicine quality problems and other medicine-related issues. Furthermore, some participants in this study provided new insights into the definition of medicine quality from different perspectives. Such insights included that a good quality medicine should be available in different dosage forms and doses to address different patients' requirements; be available in an attractive package; have been previously used and accepted by patients; is present in a well regulated market and procured from a reliable source. These new insights were not found in the results of similar studies (Syhakhang et al., 2004; Patel et al., 2009; Patel et al., 2010; Patel et al., 2012).

Most participants felt that the quality of medicines in Saudi Arabia was high to indicate their faith in the medicine regulators in the country. This could be due to the healthcare professionals' confidence in the health care system they work in, including the medication supply chain, as was reported in other studies conducted in developing

countries, and as found with nurses and patients in Laos (Syhakhang et al., 2004) and healthcare professionals in South Africa (Patel et al., 2009; Patel et al., 2012). Moreover, most participants believed that higher priced branded medicines manufactured in developed countries available in the Saudi Arabian market were better in quality than other alternatives and are, therefore, preferred by patients. This is in line with other studies conducted in developing countries. One such study found that nurses selling medicines in Laos believed that expensive medicines from a reputable manufacturer were of higher quality and advised patients to procure these medicines (Syhakhang et al., 2004). Healthcare policy makers in Sudan believed that consumers linked high price with high quality medicines (Alfadl et al., 2013). Patients in South Africa treated cheaper medicines with suspicion and also thought they were fake (Patel et al., 2010; Patel et al., 2012). Holloway, Gautam, Harpham & Takey (2002) found that patients in rural Nepal were more likely to select the more expensive brand of paracetamol.

Some participants indicated several practices associated with ensuring the quality of medicines in their settings. Such practices include checking the medicine expiry dates and storage conditions, dispensing medicines with ice bags if required, visual checks of medicine containers and communicating with the regulatory authority laboratory to ensure that specific medicines' batch numbers were analysed and cleared for patient administration. These findings did not mirror similar studies found in the literature to a large extent. Patel et al. (2009) found that healthcare professionals in South Africa identified medicine procurement from licensed suppliers, use of standard operating procedures and audits as key strategies to ensure medicine quality in South Africa. Khan et al. (2011) found that managing executives of pharmaceutical wholesalers identified local registration status, credibility of the product and reputation of the manufacturer during procurement and also considered intactness of medicines, their specification, local registration, batch and/or lot number and the name of the manufacturer during the reception of medicine consignments.

The participants in this study have discussed challenges to medicine quality in Saudi Arabia. Poor storage conditions, extreme weather conditions, poor transport conditions,

the presence of a single laboratory for medicine clearance in the country, as well as that hospitals from different organisations use different procurement practices to acquire their medicines, have all been highlighted by different participants. Such concerns about the effect of the hot weather conditions on medicine quality in Saudi Arabia might be shared with other researchers who investigated the storage conditions of community pharmacies in Saudi Arabia and found medicines stored in temperatures above the accepted standards in some community pharmacies in Riyadh (Khojah et al., 2013a). However, several recommendations were made by participants to improve the quality of medicines in Saudi Arabia. Such recommendations included laboratory analysis of medicine samples, the improvement of the national reporting system for medicine quality problems, conducting further research on the topic of medicine quality, establishing appropriate legislation for poor quality medicines, the rapid resolution of any poor quality medicine incident, the assessment of the current medicine registration process in the healthcare regulatory authority and for manufacturers to establish good practices and monitor the quality of their medicines within the market.

The results from Phase 1 of this study, in conjunction with the systematic literature review (Chapter 5), directed the development of the questions in the survey questionnaire and interview guides used for the subsequent phases. The questions about knowledge of possible causes and the impact of medicine quality problems demonstrated a clear understanding by all participants and were, therefore, deleted from future phases of the study. The participants did not comprehend the term "substandard medicines" and they were unable to translate it into Arabic. Hence, questions about substandard medicines were deleted from future phases of this study. Counterfeit medicines were successfully translated into the term "maghshoosh" in Arabic and therefore were added to the questions for the future phases of the study. Moreover, several issues emerged in the discussion about the type of medicine formulation for quality concern, the type of medicine therapeutic class of quality concerns and the number of annual incidents of suspicion of poor quality medicines in their practice. Hence, questions about these emerging issues were developed and added for the following phases of this study.

Limitations and strengths of this phase of the study

The findings from this study must be considered within their limitations. It was only a single focus group discussion with a limited number of participants and therefore findings cannot be generalised. All the participants in this study were pharmacists, which might suggest a different possible outcome if other perceptions of alternative healthcare professionals were explored. The use of a focus group method could limit in-depth understanding of various opinions, particularly from some shy participants in a group dynamic. However, the researcher attempted to minimise this effect by ensuring that individuals shared their opinion on topics equally, where possible. Nevertheless, this study had successfully achieved its objectives. It was the first study to explore perceptions about medicine quality and their related issued in Saudi Arabia. Findings from this study could be helpful for future studies about perceptions of medicine quality and their related issues in different settings, particularly in Arabic-speaking countries.

6.7 Phase 2: Commissioners' perceptions about medicine quality and their problems within the MOI-MSD in Saudi Arabia

6.7.1 Introduction

Conventionally, counterfeit and substandard medicines have been mainly determined through laboratory testing of medicine samples (Patel et al., 2010). There have been multiple studies conducted to confirm their existence in some parts of the world (Chapter 3). However, limited studies have been conducted to understand medicine quality and their problems from a non-laboratory perspective (Chapter 5) particularly in Saudi Arabia (Chapter 6 phase 1).

6.7.2 Aim

The overall aim of this phase of the study was to investigate the commissioners' perspectives on medicine quality and related issues at MOI-MSD healthcare settings in Saudi Arabia.

6.7.3 Objectives

The specific objectives of this study includes the following:

- Explore MOI-MSD commissioners' beliefs and views about medicine quality and their problems.
- Investigate MOI-MSD commissioners' knowledge and behaviour towards medicine quality and any related problems.
- Explore commissioners' views on the potential improvements to existing policies and procedures to address the issue of medicine quality in Saudi Arabia in the context of the global market.

6.7.4 Methods

To achieve the objectives of this phase, a qualitative approach using semi-structured interviews as a method for data collection was considered appropriate. This approach allowed for flexible collection of data and achieved a greater in-depth understanding of this social phenomena (Smith, 2002; Morse & Field, 1995).

6.7.4.1 Selection of participants and study settings

The participants selected for this phase of the study were commissioners within the MOI-MSD who were purposefully selected based on having an active decision-making role in the medicine supply chain from the point of medicine selection from different manufacturers until such time as it reaches the dispensing pharmacy in any MOI-MSD primary care clinics in these settings. These participants were considered to be knowledgeable individuals who require deeper insight into their experiences regarding medicine quality and any related problems. Respondents were approached personally and recruited by the principal researcher, who explained the aim of this study, before receiving a verbal consent from them to participate at a later date convenient to them. All potential respondents agreed to participate in this study. The commissioner' interviews were conducted in their offices within familiar settings to them in an attempt to ensure the respondents' privacy and comfort before answering any questions. A commissioner information sheet (Appendix 14) was handed to all respondents prior to the interview beginning.

6.7.4.2 Development of interview guide

The semi-structured interview guide was developed based on the findings from a previous systematic literature review (Chapter 5) and a focus group study (Chapter 6 phase 1). Table 6.2 highlights the key questions in the commissioners' interview guide.

Table 6.2 Commissioners' interview guide questions in chronological order regarding their perception about medicine quality and their problem in MOI-MSD in Saudi Arabia

1. In your opinion, what is a high quality medicine?
2. What do you think of the quality of medicines available in Saudi in general?
3. What do you think of the quality of medicines available in MOI in general?
4. Have you ever experienced a medicine with doubtful quality? If yes when and how?
5. How many times a year do you come across medicines with doubtful quality?
6. If you had concerns about the quality of a medicine what would you do?
7. What medicine therapeutic class are you mostly concerned with in terms of quality?

8. What type of medicine formulation are you mostly concerned with in terms of quality?

9. What are the attributes required for a medicine to be available to your patients?

10. In your opinion, what is the relationship between price and quality of medicines?

11. In your opinion, what is the relationship between medicine quality and health outcomes?

12. In your opinion, what is a counterfeit medicine?

13. What in your opinion is the percentage of counterfeit medicines globally?

14. What in your opinion is the percentage of counterfeit medicines in Saudi Arabia?

15. What changes would you recommend to ensure the high quality of medicines?

16. What other concerns about medicines in your settings that you may have that we did not discuss?

6.7.4.3 Validity and reliability checks

Three academic members of staff at the University of Hertfordshire reviewed the interview guide questions for face validity. The interview was piloted with two post-graduate Saudi Arabian pharmacists studying at the University of Hertfordshire, who were not members of the previous phase of the study (Chapter 6 phase 1) and were asked to provide feedback on the question content, order and clarity. The outcomes from the previous phase of the study (Chapter 6 phase 1), expert feedback and pilot tests resulted in minor amendments in the wording of the final interview guide (Table 6.2).

6.7.4.4 Data collection

The period for data collection in this phase was during March 2014. All interviews were tape-recorded and conducted in the Arabic language, native to both the researcher and the respondents. Probing and follow-up questions were frequently posed to respondents to ask for further clarification and information regarding their answers. The order of questions was similar for all participants to allow for data comparability where possible and to minimise possible effects of variation in the questions order on the results (Patton, 1987; Alfadl, 2012). Demographic information of commissioners was collected

prior to the start of interviews. All interviews were conducted following an informed consent and none lasted longer than 30 minutes in this phase.

6.7.4.5 Questions and transcript translation

Interview guide questions were delivered to the commissioners in Arabic in an attempt to maximise their ability to express their thoughts freely. The questions were translated into Arabic by the principal researcher; then translated into English and back to Arabic by two bilingual native Arabic-speaking members of staff at the University of Hertfordshire and the two versions of the Arabic questions in the interview guide were compared and found to have minimal differences in some phrases. All participants were sent a copy of the interview transcripts via e-mail to ensure the accuracy of their statements and none proposed any changes. Furthermore, following the transcription and translation of the interviews, two bilingual native Arabic-speaking members of staff at the University of Hertfordshire assisted the principal researcher in validating the accuracy of translation from two randomly chosen interview transcripts and the two versions were found to be similar, with the exception of some minor differences in some of the phrases used.

6.7.4.6 Data analysis

Interview data were thematically analysed following transcription verbatim in Arabic and translation of data into English using the qualitative data analysis software NVivo, version 10 to generate major themes. The data analysis process followed a method adopted from Strauss & Corbin (1990) in five steps, as follows:

1) Interview transcripts were read and re-read to increase familiarisation with data, while taking initial notes.
2) Preliminary description and interpretation of notes was performed and codes assigned based on these interpretations.
3) The connection between the codes was identified and the pattern in the codes was developed.
4) Themes and sub-themes were determined by examining the different cluster of codes available.
5) The themes and sub-themes were examined across all interviews and predominant themes were assigned.

The principle researcher independently analysed the interview data and assigned the initial codes. The supervisor of this study coded two random interviews and reviewed the final results with minimal discrepancies in the coding and interpretation of data.

6.7.5 Results

6.7.5.1 Participants' characteristics

All commissioners (6/6) who were approached for recruitment had agreed to participate in this phase of the study (100% response rate). All commissioners were pharmacists working in the MOI-MSD. Table 6.3 presents the demographic details collected from the commissioner group in this phase of the study.

Table 6.3 Commissioners' demographic details

Participant code	Gender	Age	Education	Position title
Commissioner 1	Male	35	BSc	Manager
Commissioner 2	Male	40	BSc	Manager
Commissioner 3	Male	42	BSc	Manager
Commissioner 4	Male	43	BSc	Assistant Director
Commissioner 5	Male	42	MSc	Assistant Director
Commissioner 6	Male	50	PhD	Director

6.7.5.2 Themes

The interviews with the MOI-MSD commissioners generated seven themes as follows:

Theme 1: Knowledge and belief about medicines and their quality

All commissioners (6/6) believed that a good quality medicine was a medicine that generated a good effect.

"The one which gives you 100% desired effect within the desired time"

(Commissioner 3)

The majority of commissioners (4/6) also described a good quality medicine, in their opinion, as the brand medicine from the innovator company since they have a high reputation, more experience and have run trial studies on their products accordingly.

"The first thing is quality which is attached with brand companies because such companies are prestigious, well-known in the market, preserve their reputation, comply with GMP, market their products in their own countries…" (Commissioner 2)

The commissioners also described other characteristics of a good quality medicine less frequently, such as having a good bioavailability (3/6), good packaging (2/6), having an affordable price (1/6), being a registered product (1/6), with good stock movement (1/6), accepted by patients (1/6) and with additives from a reliable source (1/6).

The commissioners identified several sources of information regarding medicine quality. Most commissioners (4/6) identified actual experiences with medicines whether this was their personal experience, a family or friend's experience, the experience of primary care representatives, physicians or patients from the primary care clinics. Other commissioners (3/6) have identified memos or letters of product recalls distributed by the SFDA or MOH as a primary source of information about medicine quality.

"We usually know about the quality of medicines from the memos and letters we receive from SFDA and MOH" (Commissioner 3)

Theme 2: Experiences and behaviour with questionable quality medicines

The majority of commissioners' (4/6) experiences with questionable quality medicines involved a past experience of a generic medicine that did not have an effect, which was followed by a successful treatment following a switch to a brand product of the same medicine.

"I had a chest infection so I used the product… not the mother company's product … but it felt like I haven't used a medicine…it was like taking a placebo..."
(Commissioner 1)

Some commissioners (2/6) specifically recalled receiving a letter from the medicine regulatory authority in Saudi Arabia regarding generic paracetamol syrup that did not contain any active ingredient.

"The paracetamol syrup not containing any active ingredient like an empty syrup"
(Commissioner 3)

The commissioners did not agree on the frequency of poor medicine quality reports they received. Some (3/6) believed that such reports are common and are easily more than ten reports each year. Others (3/6) said that it was not common and they might receive one poor medicine quality report every one or two years.

When the commissioners were asked about their behaviour, when in doubt about the quality of any medicine, most commissioners had different answers according to the settings where such doubts occurred. In their work settings, some commissioners (3/6) would report the incident to SFDA and their higher administration. Other actions were also mentioned on single occasions (1/6), such as evaluating the medicine's stock movement and summoning the manufacturing company for discussion. On a personal level, some commissioners (2/6) would look for alternative medicines or pharmacies if necessary. Only one commissioner considered reporting the matter to the SFDA or MOH, if in doubt about a poor quality medicine outside their work settings. Moreover, one commissioner suggested that patients might not know where to report poor medicine quality incidences.

Theme 3: Perceptions about medicine quality

Most commissioners (5/6) generally perceived the quality of medicines available in the Saudi Arabian market as good or excellent. When asked to rate the quality of medicines available in the market on a scale of 10, where 10 was the best quality, the majority of commissioners (5/6) responded with answers ranging from 7 up to 10 out of 10. Some justification was provided by the commissioners for their rating, based on individual factors such as the high control of the market by the SFDA, having an open market where you could find both generic or brand medicines and the low incidences of fake

medicine in the country. However, there was one commissioner (1/6) who perceived the quality of medicines in Saudi Arabia as average with 6 out of 10 in rating, and none of the commissioners rated them poorly. Moreover, some commissioners (2/6) had a perception that medicine quality of brand medicines comes first, followed by Saudi Arabian manufactured generics, and then all other manufactured generics.

"…If you want them in order I think that the mother company is the best followed by the Saudi product and then the Arabic products…" (Commissioner 1)

The majority of commissioners (4/6) perceived the quality of medicines available in the MOI-MSD as average. When asked to rate the quality of medicines available in the MOI-MSD on a scale of 10, where 10 was the best quality, the majority of commissioners (4/6) responded with 5 up to 6 out of 10. Only one commissioner thought it was of a good quality, rating it between 7 up to 8 on a scale, where 10 is the best, and only one commissioner believed that the quality of medicines in the MOI-MSD was poor, rating it between 3 to 4 on a scale of 10. For the majority of commissioners (4/6), who thought that the quality of medicines available in the MOI-MSD was average, some justification was noted which mainly concentrates on the fact that the majority of available medicines were generics, procured from a tender system which is commonly associated with selection based on the cheapest price rather than quality, unsatisfactory reports from physicians and patients on their efficacy, and the number of product recall memos or letters they appear in, according to some commissioners.

"90-95% of letters from SFDA about failed products are generics which causes distrust of physicians and pharmacists because these letters are sent to them" (Commissioner 6)

Some commissioners (4/6) offered their perspectives on patients' perception about medicine quality. Patients could complain and reject their generic medicines and ask for brand medicines according to some (3/6) commissioners. One commissioner was of the opinion that patients always complained and that, when they did, their complaint is taken seriously. Additionally, one commissioner suggested that patients could confuse manufacturing errors with counterfeit medicines.

"I remember once that a company's suspension… stuck to the bottle…we cannot say that this is counterfeiting but manufacturing errors, although the patient would perceive that as counterfeiting" (Commissioner 5)

Theme 4: Price, health outcome and quality relationship in medicines

The majority of commissioners (4/6) believed that there was a relationship between medicine quality and price, where the higher the medicine price, the higher the quality of medicine you received. One commissioner stated that they did not believe such a relationship existed between medicine quality and price. One other commissioner did not know what the relationship between medicine quality and price was.

"There is a common understanding among people that high price means high quality, and a common understanding among specialists that high quality must be expensive" (Commissioner 5)

Most commissioners (5/6) believed that there was a relationship between medicine quality and health outcomes, where the higher the medicine quality, the better the health outcomes. One commissioner did not believe that such a relationship existed between medicine quality and health outcomes.

Theme 5: Counterfeit medicines

The majority of commissioners (5/6) described counterfeit medicine in terms of problems associated with the active pharmaceutical ingredient. Some commissioners (3/6) emphasised that a counterfeit medicine was a medicine that had no active pharmaceutical ingredient, while other commissioners (4/6) described it as a change in the percentage of the active pharmaceutical ingredient and presence of undeclared additives (1/6). On several occasions, counterfeit medicines have been described by some commissioners (3/6) as not complying with the physical attributes required for the medication such as disintegration problems, change in colour or change in odour, highlighting problems with weather and storage conditions.

"A counterfeit medicine could be stored in poor conditions although the manufacturing was of good quality but the poor storage could lead to certain precipitations or odour"

(Commissioner 2)

Some commissioners (3/6) described a counterfeit medicine in terms of effect, such as lack of effect, toxic effect or different effect than that which is described on the medicine package or desired by the patient.

"As I see it, it wouldn't give me its effect. As you know, what is written or desired I didn't feel so you feel that this medication is fake or bogus…" (Commissioner 4)

Few commissioners (2/6) described counterfeit medicines in terms of packaging problems such as a deliberate change in expiry date and fake packaging. One commissioner described the term counterfeiting by emphasising that it must be intentional and should not be confused with manufacturing errors. Furthermore, one commissioner described the process of companies keeping their medications in unsuitable containers as counterfeiting, since it employs the deception of the uninformed consumer.

"A medicine that should be stored in glass containers…then you find it in plastic containers this is also counterfeiting…" (Commissioner 1)

When commissioners were asked about their estimation of the prevalence of counterfeit medicines on a global scale, mixed responses were given. Some commissioners (2/6) estimated that it could reach 20-40%. Some commissioners (2/6) believed that the counterfeit medicine prevalence rate is between 0-10% globally. Other commissioners (2/6) believed that 50% or more of global medicines were counterfeit.

Similarly, when commissioners were asked about their estimation of the prevalence of counterfeit medicines in Saudi Arabia, mixed responses were also obtained. Some commissioners (2/6) estimated that it could reach 20-40%. Some commissioners (2/6) believed it was between 0 to 10% in Saudi Arabia. Other commissioners (2/6) estimated that 50% or more of the medicines available in Saudi Arabia were counterfeit.

Theme 6: Challenges to medicine quality

Most commissioners (4/6) identified the tender-based medicine procurement system as a challenge to medicine quality in their setting since it was largely focused on the cheapest price rather than the medicine quality.

"… The procurement system does not support me in the selection of medicines; there should be a section about quality" (Commissioner 2)

Several commissioners (3/6) identified limited reports about medicine quality problems they received from MOI-MSD staff as a challenge to medicine quality in their settings.

"If there were concerns, it matters to me that there would be forms for example post marketing surveillance, which is completed by specialists. This is our biggest support however the feedback is really not positive…they do not write to us although the forms are available to them…" (Commissioner 6)

Some commissioners (2/6) described the limited budget available for medicine procurement in the MOI-MSD as a challenge in these settings as it would minimise their ability to procure higher quality brand medicines in their opinion.

"The problem is that you are restricted with a limited budget that is the problem" (Commissioner 4)

There were other less common challenges to medicine quality that were identified by commissioners, such as the unknown storage conditions of medicines received from companies, lack of post-marketing analysis of medicines, absence of quality guidelines to follow, generic company representatives only discussing medicine prices with local MOI-MSD staff and the outdated MOI-MSD medicine formulary: all were highlighted by commissioners on an individual basis.

Theme 7: Recommendations to ensure high medicine quality

Participants in this phase of the study had a wide range of recommendations to ensure medicine quality in Saudi Arabia. The major recommendations from the commissioners' group included activating the role of the SFDA in monitoring and analysing medicines (2/6) and implementing changes to the current medicine procurement system (2/6).

"The patients' daily bed cost today is much more expensive than payment for a good medicine…when you are procuring a good medicine you are actually saving money"
(Commissioner 1)

Other individual recommendations by commissioners included increasing the medicine procurement allocated budget, the establishment of independent laboratories for medicine analysis, sending MOI-MSD staff to inspect GMP compliance of pharmaceutical manufacturers and the establishment of an awareness programme or advertisement about medicine quality problems (2/6).

6.7.6 Discussion

All commissioners in this phase of the study believed that a good quality medicine was a medicine that resulted in a good effect for the patient. This result is in line with findings from other studies conducted with nurses in Laos (Syhakhang et al., 2004), healthcare professionals in South Africa (Patel et al., 2009; Patel et al., 2012) and the findings from a study with Saudi Arabian pharmacists in the UK (Chapter 6 phase 1). Most commissioners indicated that a good quality medicine was a brand medicine from an innovator company. This finding mirrors other opinions regarding brand medicines' superiority over generic medicines, held by some pharmacists within the literature (Babar et al., 2011; Basak & Sathyanarayana, 2012) and the findings from the previous phase of this study (Chapter 6 phase 1). In one study, 65% of pharmacists in New Zealand stated that the original brands had higher quality than their generic substitutes (Babar et al., 2011). Patients had mixed views about generics in the literature. Some reported accepting it (Heikkilä et al., 2011) while others believed they were inferior in quality (Kjoenniksen I, Lindbaek M, Granas, 2006; Babar et al., 2008; Albarraq, 2013). Physicians were also reported to have mixed views where some were supportive of the

quality of generic medicines (Kersnik & Peklar, 2006; Alghasham, 2009; Heikkilä et al., 2007; Tsiantou et al., 2009) and others were concerned about the quality of generic medicines to some degree (Hassali et al., 2006; Shrank et al., 2011; Chua et al., 2010).

Most commissioners in this study believed that the medicine quality in Saudi Arabia was high. This result is in line with findings from other studies conducted in developing countries where nurses, pharmacists and physicians believed that the quality of medicines was high in their own countries (Syhakhang et al., 2004; Patel et al., 2009; Patel et al., 2012) and the findings from the previous phase of this study (Chapter 6 phase 1). However, most commissioners believed that the quality of medicines in the MOI-MSD was less than what is available in the Saudi Arabian market generally. Some commissioners justified these views as resulting from the tender-based system for medicine procurement which favours cheaper generic medicines, which in turn receive the highest numbers of product-recall memos from the healthcare regulators in Saudi Arabia, and physician or patient complaints.

Counterfeit medicines were defined by most commissioners in this study in terms of problems associated with the active pharmaceutical ingredient. This finding does not mirror results from other studies, for example, where the commissioners in Sudan predominantly described a counterfeit medicine as one that entered the country illegally (Alfadl et al., 2013). Although the commissioners in this study clearly understood that a counterfeit medicine could mean the absence of the active pharmaceutical ingredient or the presence of the wrong active ingredient, there was less emphasis in their answers on the deliberate nature of the act, the importance of medicine package details and the authentication of medicine source, when compared with the widely accepted WHO definition of counterfeit medicines (WHO, 1999a). It was found that the majority of commissioners in this study predicted that the counterfeit medicine prevalence rate on a global scale was considerably higher than the WHO estimation of 10% (Cockburn et al., 2005; Heyman & Williams, 2011; Ziance, 2008). Moreover, when asked about their estimation of the counterfeit medicine prevalence rate in Saudi Arabia, mixed opinions were evident. Around one third of the commissioners agreed with the SFDA estimation that counterfeit medicines were almost non-existent in the country, with a prevalence

rate between 0 to 10% (Arabnews, 2010). One third of the commissioners estimated that counterfeit medicines were 20 to 40% prevalent in Saudi Arabia, in agreement with media prediction in the country (Saudi Gazette, 2011). Furthermore, one third of commissioners predicted that 50% or more of medicines in Saudi Arabia were counterfeit, to exceed any previous estimation. It remains a possibility that the limited understanding of what a counterfeit medicine was could have resulted in the higher estimation of their prevalence in this study.

Commissioners in this phase of the study identified several challenges to medicine quality. Most commissioners highlighted the tender-based system for medicine procurement as a challenge to medicine quality in their settings, as it favoured lowest price rather than quality, in their opinion. Perhaps the wide belief shared among the participants in this study about their preference for brand innovator products and their perception of their superior quality could have influenced such perceptions about challenges to medicine quality. However, the tender system for medicine procurement was not identified as a challenge to medicine quality in the results obtained from the previous phase of this study (Chapter 6 phase 1). Moreover, limited reporting of medicine quality problems by healthcare staff was another major challenge identified by half of the commissioners in this phase of the study. Similar results concerning poor communication among healthcare staff regarding medicine quality reports have been found in other studies (Patel et al., 2009). In response to these medicine quality concerns, the participants in this phase of the study have shared some recommendations to ensure and improve medicine quality in the MOI-MSD. It has been suggested that the improvement of medicine monitoring, particularly within SFDA and improvements to the current tender-based system, which was predominantly based on cheapest price and did not include a quality element, would have improved the quality of the medicines available to patients.

Limitations and strengths of this phase of the study

This present interview phase of the study has several limitations. The findings from this study cannot be generalised to all MOI-MSD healthcare staff, considering the small number of the sample frame and sample size. However, generalisibility has not been the

aim of this phase of the study as we aimed to explore different opinions and conduct in-depth analysis of the available information from the executives responsible for medicine supply in the MOI-MSD. Another limitation of this study could be the absence of female participants in this phase of the study. This limitation was not avoidable since the entire sample frame in this phase of the study was male. Furthermore, some questions required answers from the respondents' past experiences and could be subject to recall bias. Moreover, other questions asked respondents about their practices regarding medicine quality issues that cannot be verified in the absence of an observational study. The small number of the sample frame available for this phase of the study has prevented seeking data saturation. Nevertheless, this study was among the very few studies that examined medicine quality issues from the perspective of different stakeholders. To the researcher's knowledge, it was the first study exploring such issues in Saudi Arabia and MOI-MSD settings. The next phase of this study examined the MOI-MSD patients' perception about medicine quality and any related problems, in order to improve the understanding of the phenomena.

6.8 Phase 3: Patients' perceptions about medicine quality and their related issues within the MOI-MSD in Saudi Arabia

6.8.1 Introduction

It has been previously established that studies addressing perceptions about medicine quality and their problems are severely lacking worldwide (Chapter 5). Stakeholders' perceptions about medicine quality and their problems have been found to be non-existent in Saudi Arabia (Chapter 5). The previous phases of this study have resulted in exploration of the scope of stakeholders perceptions about medicine quality and any related problems in Saudi Arabia, the development of questions for interview guides and survey questionnaires (Chapter 6 phase 1) and examined the perceptions of MOI-MSD commissioners (Chapter 6 phase 2) regarding medicine quality and any related issue.

6.8.2 Aim

The overall aim of this phase of the study was to investigate the patients' perspectives on medicine quality and related issues at MOI-MSD healthcare settings in Saudi Arabia.

6.8.3 Objectives

The specific objectives of this study includes the following:

- Explore patients' beliefs and views about medicine quality and any related issues.
- Investigate the patients' knowledge and behaviour towards medicine quality and any related issues.
- Explore potential improvements to existing policies and procedures to address the issue of medicine quality in Saudi Arabia in the context of the global market.

6.8.4 Methods

A qualitative approach using semi-structured interviews as a method for data collection was used in this phase of the study in order to obtain a greater in-depth understanding of the research problem (Smith, 2002; Morse & Field, 1995). Furthermore, using an

interview method for data collection would allow for the inclusion illiterate patients into the sample frame.

6.8.4.1 Selection of participants and study settings

As previously mentioned in the introduction part of this thesis (Chapter 1), the MOI-MSD operates 18 primary clinics outside the capital city of Riyadh, in addition to 3 specialist primary care clinics in Riyadh. The sample frame for this interview phase of the study included MOI-MSD patients from two specialist primary care clinics in Riyadh and one in Jeddah city, which are the two most populated cities in Saudi Arabia (Appendix 2). Patients were conveniently selected based on their actual visits to the selected primary care clinics during the data collection period. The only exclusion criteria applied for recruitment in this phase of the study were patients below the age of 18 years old. Both male and female participants were recruited in this study in order to enhance patient representation from both genders in the final results.

Patient recruitment was carried out by several means. The principal researcher personally approached some, whilst collaborating physicians and pharmacists initially approached others. The principal researcher explained the aim of the study to all respondents and they were handed a hard copy of the participant information sheet (Appendix 14). Interviews were conducted in vacant physicians' offices in each setting, in order to be in close proximity to collaborating physicians to ensure patients' privacy and also to minimise the patients' effort to reach the interview site. The principal researcher introduced himself as a scholar from the University of Hertfordshire in the United Kingdom to all respondents and explained that this work was for academic purposes only, in an attempt to achieve honest answers. All respondents were encouraged to speak freely without fear, as there will be no action based on their answers and they were reminded that the results would be anonymised. All interviews were conducted immediately following the respondent's agreement to participate by signing an informed consent (Appendix 16).

6.8.4.2 Development of interview guide

The semi-structured interview guide was developed based on the findings from a previous systematic literature review (Chapter 5) and a focus group study (Chapter 6

phase 1). The interview guide used in this phase of the study was mostly similar to the interview guide used with the commissioners' group (Chapter 6 phase 2). A few questions were added to the patient interview guide in order to identify patients' expectations from their medicine, the source of their medicines, the type of medicines they were using and the source of information regarding their medicines. Furthermore, some questions were only available for the commissioner's interview guide and not in the patient's interview guide since they were irrelevant to this sample frame. Examples of such deleted questions included questions about the frequency of annual doubts about the quality of medicines, the therapeutic classes and formulations of most quality concerns.

6.8.4.3 Data collection

The interviews were conducted in the period between March 2014 and April 2014. All interviews were tape-recorded and conducted in the Arabic language, native to both the researcher and the patients. Probing and follow-up questions were frequently posed to respondents to ask for further clarification and information regarding their answers. The question order was similar for all participants, to allow for data comparability where possible and to minimise the possible effects of variation of question order on the results (Patton, 1987; Alfadl, 2012). Demographic information was collected prior to the start of the interviews. All interviews were conducted following the signature of a patient informed consent form and none lasted more than 30 minutes in this phase. The recruitment of participants in this phase continued until no new themes emerged with the final three interviews.

6.8.4.4 Validity and reliability checks

The validity and reliability check were conducted using a similar method to the previous interviews with the commissioners in the MOI-MSD (Chapter 6 phase 2). In addition, the interview guide was piloted with two patients in Saudi Arabia, who were not members of the sample frame, through Skype (www.skype.com) internet-based video/audio recording method and they were requested to provide feedback on the question content, order and clarity.

6.8.4.5 Questions and transcript translation

The interview guide was developed in Arabic since patients in these settings cannot be assumed to have adequate proficiency in the English language. The process of translation and validation of the accuracy of translation was conducted with a similar approach to a previous phase of this study (Chapter 6 phase 2).

6.8.4.6 Data analysis

Interview data were thematically analysed following transcription verbatim in Arabic and translation of data into English using the qualitative data analysis software NVivo, version 10 to generate major themes. The data analysis and coding of themes was similar to that reported in a previous phase of the study (Chapter 6 phase 2).

Furthermore, the relationship between the patients' perceptions about medicine quality in the MOI-MSD and some sociodemographic variables such as age, gender, education, occupation and types of medicines used was statistically examined. The Chi-square and Fishers's exact tests were conducted using SPSS version 21 where 95% confidence interval (CI) was considered statistically significant.

6.8.5 Results

6.8.5.1 Participant characteristics

In total, 53 patient interviews were conducted in this phase of the study to achieve a response rate of 66% from the total number of patients approached for recruitment. A description of the recruited patients' characteristics can be found in Table 6.4.

Table 6.4 Patients' characteristics in the interview phase of the study

Category	Subcategory	Number (%)
Location of interview	Riyadh	44 (83%)
	Jeddah	9 (17%)
Gender	Male	35 (66%)
	Female	18 (34%)
Age	18-19	3 (6%)
	20-29	17 (32%)
	30-39	12 (23%)
	40-49	11 (21%)
	50-59	5 (9%)
	60 or more	5 (9%)
Education	None	6 (11%)

	Primary	3 (6%)
	Intermediate	5 (9%)
	Secondary	23 (43%)
	Diploma	3 (6%)
	BSc	12 (23%)
	MSc	1 (2%)
Occupation	Unemployed	10 (19%)
	Retired	6 (11%)
	Civilian employee	7 (14%)
	Military employee	24 (45%)
	Student	6 (11%)
Type of medicines used now	Chronic disease medicines	22 (42%)
	Acute disease medicines	27 (51%)
	Not using medicines now	4 (7%)
Source of patients' medicines	MOI-MSD only	11 (21%)
	MOI-MSD and other public hospitals	12 (23%)
	MOI-MSD and private pharmacies	16 (30%)
	Private pharmacies only	9 (17%)
	Public or private hospitals	5 (9%)

6.8.5.2 Themes

The interviews with MOI-MSD patients generated eight themes as follows:

Theme 1: Knowledge and belief about medicines and their quality

A significant number of patients (14/53) did not know the name of their medicines. Male patients, in particular, (11/35) showed less knowledge about their medicine names when compared with female patient (3/18). Moreover, patients with no or lower educational levels were found to have lower knowledge about their medicine names (6/14) compared with patients with higher educational levels (8/36). Furthermore, a considerable number of chronic patients (7/22) did not know the names of their medicines when compared with patients taking medicines for acute conditions (6/27).

Most patients (29/53) described a good quality medicine in terms of its effect, which should be ideally rapid with minimal side effects in their opinion.

"That means that is fast in effect for the disease…" (Patient 43)

Patients identified other characteristics of good quality medicines. Some patients (7/53) indicated that a good quality medicine was the one recommended by their physician. This understanding of high quality medicines was particularly noted with patients aged 50 years or older (5/10) and patients with no education (3/6). Other patients (7/53) believed that a good quality medicine has good manufacturing status. There were other answers reported by patients such as not manufactured locally (2/53), having a previous

successful experience with it (2/53), was appropriate for the disease (2/53), has a high price (1/53), accepted by their body (1/53), had strong dose (1/53), diabetes medicines (1/53) and medicines recommended by the pharmacist (1/53). Furthermore, there were some patients (5/53) who did not know what a good quality medicine was.

"It depends on the company…I would ask the advice of the doctor most importantly" (Patient 5)

Patients also shared some of their beliefs about medicines in general and medicine quality in particular. Some patients (6/53) expressed their opinion that medicines did not work similarly for all patients. A number of patients (11/53) believed that the quality of medicines was different between different hospitals in Saudi Arabia and other patients (12/53) indicated that the quality of medicines differs according to their manufacturers. There were some patients (3/53) who believed that the higher the strength of a medicine, the more likely that it had better quality and generated better effect.

"Every hospital is different…some of my relatives get treatment in the National Guard hospital and Ministry of Defense hospital and they are dispensed better and more effective medicines that would heal your condition rapidly" (Patient 2)

Theme 2: Experiences and behaviour with questionable quality medicines

Some patients (13/53) shared some experiences with medicines which did not give them the desired effect and therefore they questioned their quality.

"In the governmental hospital, I took medicines that were not that good ... I then went to a private clinic and got treatment on my expense …and I felt better" (Patient 26)

The majority of patients (23/53), however, did not have any past experiences with questionable quality medicines, specifically patients with no or lower educational levels (9/14). A few patients (3/53) did not recall such experiences with doubtful quality

medicines. Some patients (8/53) shared their experiences with medicine side effects to describe their encounters with medicines with questionable quality.

"Once I was getting treatment from a psychiatric hospital and the psychiatry medicines would worsen your case so I didn't use it. I would take the medicine bag from here and throw it from here because I felt very tired and sleepy when I took them and I have children so I need to keep moving" (Patient 16)

Patients reported a wide range of behaviour when in doubt about the quality of a medicine. The majority of patients (37/53) reported that they would stop taking the medicine immediately. Some patients (22/53) said that they would ask their physician for advice before taking any action, which was specifically found in patients aged 50 years or older (7/10) and patients with no or lower levels of education (9/14). Other patients (12/53) indicated that they would look for an alternative medicine. There were a number of patients (6/53) who would not take any action and a similar number (6/53) who would inform other medicine users to warn them about their experience. There were also less common types of patient behaviour when in doubt about the quality of medicines, such as informing the Authority (4/53), throwing the medicine away (4/53), asking the pharmacist for advice (3/53), reading the medicine leaflet for information (1/53) and not accepting to receive a medicine from the pharmacy, if they had any doubt about its quality.

"I would go back to the doctor and stop the medicine and inform the doctor…" (Patient 1)

Theme 3: Perceptions about medicine quality

Most patients (31/53) generally perceived the quality of medicines available in the Saudi Arabian market as good or high. They rated the quality of medicines available in the market between 7 up to 10, on a scale of 10 where 10 was the best quality. Female patients in particular (14/18) and patients with no education or limited education (8/14) had mostly rated the quality of medicines in Saudi Arabia as good or excellent. Some patients (15/53) rated the quality of medicines as average between 5 up to 6 on the same

scale. Only a few patients (5/53) rated the quality of medicines in Saudi Arabia as poor or unacceptable, ranging from 1 to 4 on a similar scale. There were also a few patients (2/53) who did not know how to rate the quality of medicines in Saudi Arabia.

"In the Security Forces, they are excellent and also in Saudi" (Patient 48)

Similarly, most patients (38/53) perceived the quality of medicines available in the MOI-MSD as good or high, rating them between 7 up to 10, on a scale of 10 where 10 was the best quality. Female patients in particular (15/18) and patients with no education or limited education (9/14) have favourably rated the quality of medicines in the MOI-MSD as good or excellent. Some patients (6/53) perceived the quality of medicines available in the MOI-MSD as average with ratings from 5 to 6 on the same scale. A few patients (5/53) believed that the quality of medicines in the MOI-MSD was poor or unacceptable by rating it from 1 to 4 on the scale. There were also a few patients (4/53) who did not know how to rate the quality of medicines in the MOI-MSD.

"The medicines in the Ministry of Interior and some outside primary clinics do not depend on quality of the medicine but rather on the cheap medicine price" (Patient 2)

When patients were asked about their perceptions about the quality of the medicines they were using, the majority (34/53) rated them as good or high, ranging from 7 to 10 on a scale where 10 was the best. Some patients (11/53) rated them as average, ranging from 5 to 6 on a scale where 10 was the best. Only two patients rated their medicine as poor, ranging from 1 to 4 on the scale, and six patients did not rate the quality of their medicines.

"I would give it 7 because I have been using this medicine for a while with the same result and I am hoping for more" (Patient 38)

Theme 4: Price, health outcome, disease and quality relationship in medicines

The majority of patients (27/53) believed that there was a relationship between medicine quality and price where the higher the medicine price, the higher the quality of a medicine. Some patients (17/53) stated that they did not believe such a relationship

existed between medicine quality and price. Female patients (9/18), in particular, did not associate medicine price with its quality when compared with male patients (8/35). A few patients (8/53) did not know what the relationship between medicine quality and price was.

"What is common among people is that the expensive medicine has higher quality…" (Patient 42)

Most patients (35/53) believed that there was a relationship between medicine quality and health outcomes where the higher the medicine quality, the more likely health outcomes would be better. A few patients (5/53) did not believe that such a relationship existed. Several patients (13/53) indicated that they did not know if there was a relationship between medicine quality and health outcomes.

"They have a relationship. If the quality increased, the recovery would be better and wouldn't take long time" (Patient 53)

There were a few patients (4/53) who perceived a relationship between medicine price and the severity of the disease. They believed the medicine price would be more expensive if the disease was more severe.

"It depends on the type of disease. The most expensive medicines are for very sick people like cancer, blood pressure and diabetes and surely their cost is higher…" (Patient 19)

A number of patients (14/53) have expressed their opinion that medicine prices were expensive. In particular, patients from Jeddah (5/9) who were using medicines to treat their chronic conditions (4/9) shared this view.

Theme 5: Counterfeit medicines

Some patients (14/53) described a counterfeit medicine in terms of effect such as lack of effect, toxic effect or different effect than what was described on the medicine package

or desired by the patient. Other patients (10/53) believed that a counterfeit medicine was a medicine with a problem in manufacturing with minimal description of the type of problem. Moreover, some patients (5/53) described counterfeit medicines as fake copies of the original medicine. Some patients (3/53) described a counterfeit medicine as one from an unreliable source. There were a few patients (2/53) who described them as non-registered or non-authorised medicines. Furthermore, one patient described the process of companies keeping their medications in unsuitable containers as counterfeiting since it employed the deception of the uninformed consumer.

"...If they have no benefit and cause harm then these are counterfeit..." (Patient 26)

Notably, there were some answers in the patients' group that would suggest a degree of confusion between their understanding of counterfeit medicines and other medicine related issues. Some patients (4/53) thought that cheaper generic medicines were counterfeit. Other patients (4/53) believed that expensive medicines were counterfeit. Expired medicines were perceived as counterfeit by some patients (5/53). There were a few patients (2/53) who described counterfeit medicines as medicines stored in poor conditions. One patient thought that counterfeit medicines were medicines with side effects. Furthermore, there were some patients (12/53) who did not know what a counterfeit medicine was.

"It could be expired or it could be without benefit" (Patient 20)

When patients were asked about their estimation of the prevalence of counterfeit medicines on a global scale, mixed responses were given. Some patients (12/53) believed that the counterfeit medicine prevalence rate was between 0 to 10% globally, in particular from the female patients' perspective (7/18). Other patients (18/53) estimated that it could reach 20 to 40%. Several patients (15/53) believed that 50% or more of global medicines were counterfeit. Furthermore, there were a number of patients (8/53) who did not know what the prevalence of counterfeit medicine was on a global scale.

Similarly, when patients were asked about their estimation of the prevalence of counterfeit medicines in Saudi Arabia, mixed responses were also given. Some patients (17/53) believed it was between 0 to 10% in Saudi Arabia. Other patients (19/53) estimated that it could reach between 20 to 40%. Several patients (11/53) estimated that 50% or more of the medicines available in Saudi Arabia were counterfeit. Additionally, there were a number of patients (6/53) who did not know how to answer this question.

There were some additional patient comments regarding counterfeit medicines in Saudi Arabia. A few patients (4/53) indicated that the problem of counterfeit medicines had increased recently in the country. Other patients (4/53) believed that counterfeiting in the country was not in medicines but rather in cosmetic and herbal products.

"In Jeddah they found a warehouse that has counterfeit medicines smuggled from abroad… It happened 2 or 3 times and it was on the television on the news"
(Patient 26)

Theme 6: Challenges to medicines and their quality

The patients identified several challenges to medicine quality in this phase of the study. Some patients (11/53) highlighted medicine non-availability at the primary clinics as a challenge to medicine quality since it required them to buy medicines out of their own pocket elsewhere. This issue was raised by a higher number of patients in interviews conducted in Jeddah (4/9) than interviews conducted in Riyadh (7/44). Furthermore, chronic patients reported medicine non-availability more often (7/22) than patients taking medicines for acute conditions (4/27).

"…Especially the diabetes tablet, I have been buying it for 3 months on my expense because it is not available" (Patient 14)

Some patients (8/53) voiced concerns about the difficulty they found when they wanted to report medicine quality problems.

"If I went back to the pharmacy, they wouldn't accept anything from me. If I went to the Ministry of Interior they wouldn't respond to me. The only option I have is to throw it away" (Patient 18)

Some patients in this study identified several barriers that might not be directly related to medicine quality within the MOI-MSD services. The majority of barriers identified by patients (12/53) focused on the distant locations of primary care clinics and their limited opening times. Other patients (3/53) believed that hospital appointments were taking too long. A few patients (2/53) believed that pharmacists in the MOI-MSD were dispensing more than the required amounts of medicines to patients. One patient indicated that the emergency first aid at the primary clinic was slow and another patient reported that there was no emergency reception at their clinic.

"…The working hours also if I get here after a traffic jam at around 12 they would say we are closed go and come back in the afternoon…" (Patient 16)

Theme 7: Recommendations to ensure high medicine quality

There were several recommendations from the patient group to ensure medicine quality, although a considerable number of patients (11/53) did not have any recommendations. Improving medicine monitoring was recommended by some patients (13/53). Others (4/53) recommended the analysis of medicine samples and procurement from international pharmaceutical companies instead of local manufacturers. There were other less common recommendations, such as ensuring good storage conditions (2/53), ensuring date of expiry and product information was correct (2/53), that governmental medicines should have a unique identifying symbol on medicine packages (1/53), to have only one generic option to each brand medicine (1/53) and to improve supply and demand forecast to avoid having excess medicines or shortages (1/53).

"There should be high monitoring in hospitals and particularly in primary clinics" (Patient 42)

"To have contracts with global pharmaceutical companies that are known would be better" (Patient 2)

Theme 8: Patients' trust

The majority of patients (29/53) expressed their complete trust in their physicians at the MOI-MSD and (22/53) of them indicated that they would consider their advice before taking any medicines. Patients with chronic conditions, in particular, (16/22) expressed trust in their physicians on more occasions than patients taking medicines for acute conditions (11/27). However, only a small number of patients (4/53) expressed similar feelings of trust in their pharmacist and only two patients (2/53) highlighted that they would consider a pharmacist's advice before taking their medicine. Patients in this study also considered personal experience (5/53) and a friend or family experience (4/53), as a source of information they trusted, before using medicines.

"The doctor has better background knowledge about quality and price" (Patient 17)

6.8.5.3 Statistical analysis

The statistical analysis that explored the relationship between the patients' perceptions about medicine quality and their sociodemographic data did not show any statistical significance. Further details can be found in Table 6.5.

Table 6.5 Relationship between patients' perception about medicine quality in the MOI-MSD and their sociodemographic data

Characteristic	P-value
Gender	.138
Age	.720
Education	.258
Occupation	.702
Type of medicines used	1.000

6.8.6 Discussion

The majority of patients in this phase of the study understood medicine quality based on their effect. This finding was similar to other patient reports in developing countries (Patel et al., 2010; Patel et al., 2012) and our findings from previous phases of this study with Saudi Arabian pharmacists in the UK (Chapter 6 phase 1) and MOI-MSD commissioners (Chapter 6 phase 2). However, only a few patients associated a good quality medicine with a brand innovative company, which is in contrast with our findings from a previous phase of this study with MOI-MSD commissioners (Chapter 6 phase 2).

Most patients believed that medicine quality in Saudi Arabia was good or high. This result is in line with findings from other studies conducted with nurses, pharmacists, physicians and patients in developing countries (Syhakhang et al., 2004; Patel et al., 2009; Patel et al., 2010; Patel et al., 2012) and the findings from a previous phase of this study with Saudi Arabian pharmacists in the UK (Chapter 6 phase 1) and MOI-MSD commissioners (Chapter 6 phase 2). However, there was no agreement between the MOI-MSD commissioners (Chapter 6 phase 2) and patients regarding their perception about the quality of medicines in the MOI-MSD settings. Only a few patients believed that the quality of medicines in the MOI-MSD was less than what is available in the Saudi Arabian market when compared with the MOI-MSD commissioners' group (Chapter 6 phase 2). Furthermore, the association between patients' demographic information and their perception about medicine quality in the MOI-MSD was found to be statistically insignificant. Therefore, it was not possible to statistically relate such demographic information with their perception about medicine quality in this sample.

Around half of the patient group believed that high quality medicines were the expensive options. Patients were reported to have similar beliefs about the relationship between medicine price and quality in other studies (Holloway et al., 2002; Syhakhang et al., 2004; Patel et al., 2010; Patel et al., 2012; Alfadl et al., 2013). However, this belief was found to be more prevalent in the MOI-MSD commissioner' group (Chapter 6 phase 2) when compared with the current patient phase of the study.

Most patients in this study described a counterfeit medicine in terms of medicine manufacturing problems and lack of or toxic effect. This result was similar to some degree to the findings from the interviews with MOI-MSD commissioners' phase of the study (Chapter 6 phase 2). Although patients were not expected to have a correct and accurate definition of counterfeit medicines due to their technical nature, it was important for the purpose of this study to explore their understanding of counterfeit medicines before they were asked about their prediction of the counterfeit prevalence rate in Saudi Arabia and on a global scale. However, the patients' estimations of the prevalence of counterfeit medicine globally and in Saudi Arabia were found to be similar to the commissioners' estimation in the previous phase of the study (Chapter 6 phase 2). Around one third of patients believed that the counterfeit medicine prevalence rate was minimal in the country: between 0 to 10%. One third of patients estimated that counterfeit medicines were 20 to 40% prevalent in Saudi Arabia. Furthermore, one third of the patients predicted that 50% or more of medicines in Saudi Arabia were counterfeit.

The patients in this phase of the study identified several challenges to their medicine experience and to their medicines' quality. Some patients reported non-availability of medicines that they were prescribed at the MOI-MSD settings. However, only one of the commissioners in the previous phase of the study (Chapter 6 phase 2) identified medicine availability as a challenge to medicine quality in their practice. This could be potentially dangerous, as it would probably mean extra financial burdens on patients to procure such medicines elsewhere or, in a worst case scenario, could mean that patients may be vulnerable to other medicines that cannot be verified in terms of quality. Similar to the findings from the commissioners' interviews (Chapter 6 phase 2), concerns were raised by some patients about the difficulty of reporting medicine quality problems in MOI-MSD settings. Furthermore, other issues were raised by patients in this phase of the study and were not reported in the commissioners' interviews (Chapter 6 phase 2), such as the inaccessibility of some primary care clinics in terms of distant locations and inconvenient opening times.

Patients' trust in their physicians was clearly described by most patients in this phase of the study. However, only a small number of patients expressed much trust in their pharmacist's competency and some clearly stated that they do not trust their pharmacists. A gap in the relationship between pharmacists and patients was noted and required that the next phases of this study to address possible reasons for such beliefs and possible changes to increase the patients' trust in pharmacists working in the MOI-MSD settings.

Limitations and strengths of this phase of the study

This present interview phase of the study has several limitations. The findings from this study cannot be generalised since patient recruitment was from only three primary care clinics in two major cities in Saudi Arabia. However, generalisibility has not been the aim of this study as we aimed to explore different opinions and conduct in-depth analysis of the available information.

Moreover, it was noted from the patient interviews that most of them had been seeking treatment in other public healthcare providers in Saudi Arabia, which could enhance the generalisability of our finding. Furthermore, some female patients did not agree to participate in the study and some did not agree to tape recording and therefore the principal researcher took notes of their answers. Their refusal for the interview to be tape-recorded could be due to cultural barriers between genders in these settings since the principal researcher is male. The characteristics and reasons for female patients who declined participation in this study remain unknown to the researcher.

Furthermore, some questions required answers from the respondents' past experiences and could be subject to recall bias. It was not possible to send the interview transcripts back to patients since they have only provided telephone numbers in their contact details and some had little or no educational background which did not permit them to use the Internet. Our aim in this study was explorative and, therefore, we did not seek data saturation from these interviews.

Nevertheless, this study was among the very few studies that examined medicine quality issues from the perspective of different stakeholders. To the researchers' knowledge, it was the first study exploring such issues in Saudi Arabia and MOI-MSD settings from the patient's perspective. The next phases of this study explored the perspectives of pharmacists and physicians in the MOI-MSD regarding medicine quality and any related issues.

6.9 Phase 4: Pharmacists' and physicians' perceptions about medicine quality and their related issues within the MOI-MSD in Saudi Arabia

6.9.1 Introduction

Studies investigating the perceptions about medicine quality and any related issues are extremely scarce in the literature (Chapter 5). Previously, the perceptions of commissioners (Chapter 6 phase 2) and patients (Chapter 6 phase 3) have been explored within the MOI-MSD settings in Saudi Arabia.

6.9.2 Aim

The overall aim of this phase was to explore the pharmacists' and physicians' perspectives on medicine quality and related issues such as counterfeit medicines in the MOI-MSD in Saudi Arabia.

6.9.3 Objectives

The specific objectives of this study included the following:

- Establishing the MOI-MSD pharmacists' and physicians' beliefs and views about medicine quality and their related issues.
- Explore their knowledge and behaviour about medicine quality and any related problems.
- Seek the pharmacists' and physicians' views on potential improvements to the existing policies and procedures to address the issue of medicine quality in Saudi Arabia in the context of the global market.

6.9.4 Methods

6.9.4.1 Sample selection and settings

The total number of individuals in the sample frame available in the study was 293 physicians and 89 pharmacists. All 293 physicians and 71 pharmacists worked in MOI-MSD clinics according to the latest available MOI-MSD annual statistical report (Appendices 19 and 20). Eighteen additional pharmacists working in the Medical Supply Department at the MOI-MSD were added to the sample frame for their relevance to subject area of this study. The total number of pharmacists working in the Medical Supply Department was determined through personal communication with the

Department's Director in the absence of such official records. There were no physicians working at the medical supply department at the time of study.

6.9.4.2 Survey questionnaire design

A cross-sectional survey design was selected for this study to facilitate the understanding of the phenomena from the perspective of a wide range of pharmacists and physicians within our sample frame in the country. Survey questionnaires addressing medicine quality and related issues were developed in English based on a systematic literature review of similar studies (Chapter 5) and the findings from a previous phase of this study (Chapter 6 phase 1). English was chosen as the primary language for the survey questionnaires since the members of the sample frame were healthcare professionals who have a minimum of a Bachelor Degree in their subject area, which was primarily taught in English in Saudi Arabia.

The majority of questions in the questionnaire instrument were closed-ended and only a few were open-ended. A rating scale from 1 to 10, where 10 was the best or most likely, was used in some questions to measure perceptions in a similar approach to a Likert scale. The final physician questionnaire (Appendix 21) consisted of 27 questions, including 7 demographic questions, 5 questions to establish knowledge about medicine quality, 14 questions to explore perception and behaviour associated with medicine quality and one question to explore potential improvement to existing policies and procedures to address medicine quality. All respondents received every question as skip logic was not programmed in the survey. The pharmacists' survey questionnaires (Appendix 22) were similar to their physician counterparts except on some demographic and practice-related questions, such as prescribing or dispensing, to allow for group comparability.

6.9.4.3 Validity and reliability checks

The validity and reliability checks were performed in a similar method to the approach in the previous phases of this study (Chapter 6 phases 1, 2 and 3). In addition, the survey questionnaire was piloted with four pharmacy students at the University of Hertfordshire, who did not participate in the previous phase of the study (Chapter 6 phase 1).

6.9.4.4 Survey questionnaire distribution

The survey questionnaire was distributed electronically using the electronic software Survey Monkey (Portland, Oregon USA; http://www.surveymonkey.com) via a web link in WhatsApp smartphone application (Santa Clara, California USA; http://www.whatsapp.com) to all pharmacists and physicians working in MOI-MSD primary care clinics. This choice of survey distribution method was based on consultation with the Healthcare Centers Department Commissioner to ensure a higher response rate from potential participants. The Commissioner of the Healthcare Centers Department in the MOI-MSD received the customised invitation letters and web links to each survey and then distributed it to potential participants. This choice of survey distribution was considered appropriate for this sample frame since they can be assumed to be literate, with sufficient English proficiency, and it ensured the anonymity of respondents. Furthermore, the choice of an online method of questionnaire distribution was an attempt to minimise interviewer bias and social desirability bias (Bowling, 2011). The survey was available online for 8 weeks from March 2014 and required 10-15 minutes to be completed by respondents. The researcher monitored the number of responses regularly while the survey was open and weekly reminders were sent to potential respondents by the same method. Moreover, the electronic method of survey distribution was not applied to pharmacists working within the Medical Supply Department. Following consultations with the Medical Supply Director, it was agreed that hard copy survey questionnaires would ensure a higher response rate since Internet access and smart phone applications may not be available to all eligible participants in this department. The researcher distributed hard copy survey questionnaires to each section staff and agreed a time for the collection of completed copies at their convenience. This approach was selected in order to minimise the effect on participants' anonymity through multiple distribution and collection periods for hard copy self-administered survey questionnaires. The completed hard-copy survey questionnaires were subsequently entered manually into the SurveyMonkey system by the researcher. Permissions were granted prior to the start of this study from the University of Hertfordshire Ethical Committee and the General Administration of the MOI-MSD in Saudi Arabia (Appendices 9, 10 and 11).

6.9.4.5 Data analysis

Following the survey completion, results were downloaded into the latest available Microsoft Excel spread sheet and SPSS for the descriptive analysis of quantitative data. For open-ended questions, data was analysed using a content analysis approach and findings reported as numbers and percentages.

An ordinal regression model was undertook to study the relationship between the pharmacists' and physicians' perceptions about medicine quality in the MOI-MSD and the explanatory categorical variables including their gender, age, education, region of practice and years of experience working in the MOI-MSD. Ordinal regression models were chosen since the perceptions about medicine quality were initially coded as ordinal variables. The purpose for this ordinal regression model was to examine the odds ratio (OR) between these explanatory variables and having poor perception about the quality of medicines in the MOI-MSD. For example, if the OR between male physicians and poor perception about medicine quality was four, this would indicate that male physicians were four times more likely to have negative perceptions about medicine quality in these settings. The statistical analysis for the ordinal regression tests was performed using SPSS and 95% confidence intervals were considered significant.

6.9.4.6 Data coding

For Likert style questions that asked the respondents to rate their answers on a scale of 10, a five point system was used to categorically code the data as follows: ratings of 1 and 2 were coded as unacceptable; ratings of 3 and 4 were coded as poor; ratings of 5 and 6 were coded as average; ratings of 7 and 8 were coded as good and ratings of 9 and 10 were coded as excellent. However, the perception data about the quality of medicines in the MOI-MSD was recoded into rating 1 to 5 as poor quality and rating 6 to 10 as good quality in order to facilitate the ordinal regression model.

6.9.5 Results

6.9.5.1 Rate of response

A total of 58 pharmacists and 63 physicians responded to this survey questionnaire. The response rate was therefore 65% and 21.5% from pharmacists and physicians respectively.

6.9.5.2 Respondents' characteristics

Table 6.6 illustrates the demographic information of the participants in this phase of the study.

Table 6.6 Characteristics of respondents to the survey phase of the study

Category	Subcategory	Pharmacists (n=58)	Physicians (n=63)
Gender	Male	40 (69%)	53 (84%)
	Female	18 (31%)	10 (16%)
Age	20-29	15 (26%)	4 (6%)
	30-39	32 (55%)	23 (37%)
	40-49	7 (12%)	23 (37%)
	50-59	3 (5%)	11 (17%)
	60 or more	1 (2%)	2 (3%)
Practice region	Central region	30 (52%)	23 (37%)
	Western region	9 (16%)	16 (25%)
	Southern region	7 (12%)	9 (14%)
	Northern region	6 (10%)	13 (21%)
	Eastern region	3 (5%)	2 (3%)
	Not specified	3 (5%)	
Education	BSc	39 (67%)	15 (24%)
	MSc	13 (22%)	24 (38%)
	PhD	2 (4%)	9 (14%)
	Other higher education	4 (7%)	15 (24%)
Work experience in MOI-MSD	Less than one year	1 (2%)	4 (6%)
	1-4 years	16 (27%)	14 (22%)
	5-9 years	12 (21%)	12 (19%)
	10-14 years	16 (27%)	15 (24%)
	15 years or more	13 (23%)	18 (29%)

6.9.5.3 Knowledge, beliefs and views about medicine quality and their problems

The pharmacists and physicians in this study were asked to define what a high quality medicine was in an open-ended question. The majority of responses from pharmacists (n=22, 38%) and physicians (n=30, 47%) indicated that a high quality medicine was a medicine with good effect and minimal side effects. Some pharmacists (n=8, 13%) and physicians (n=1, 2%) believed that a good quality medicine was a medicine that was manufactured in optimal conditions. Several pharmacists (n=6, 10%) and physicians (n=1, 2%) considered brand medicines manufactured from innovative pharmaceutical companies as good quality medicines. Some pharmacists (n=4, 7%) and physicians (n=4, 6%) have highlighted reasonable medicine price as a key characteristic of a good

quality medicine. Furthermore, some pharmacists (n=2, 3%) and physicians (n=1, 2%) considered medicine availability as a characteristic of a good quality medicine. Respondents from the pharmacists' group described a good quality medicine as a medicine with good appearance or packaging (n=4, 7%) and being registered with the authorities (n=2, 3%). Few respondents from the physicians' group described a good quality medicine as a medicine that was accepted by the patient (n=2, 3%). Figure (6.3) illustrates the key characteristics of a good quality medicine in the opinion of pharmacists and physicians in this phase of the study.

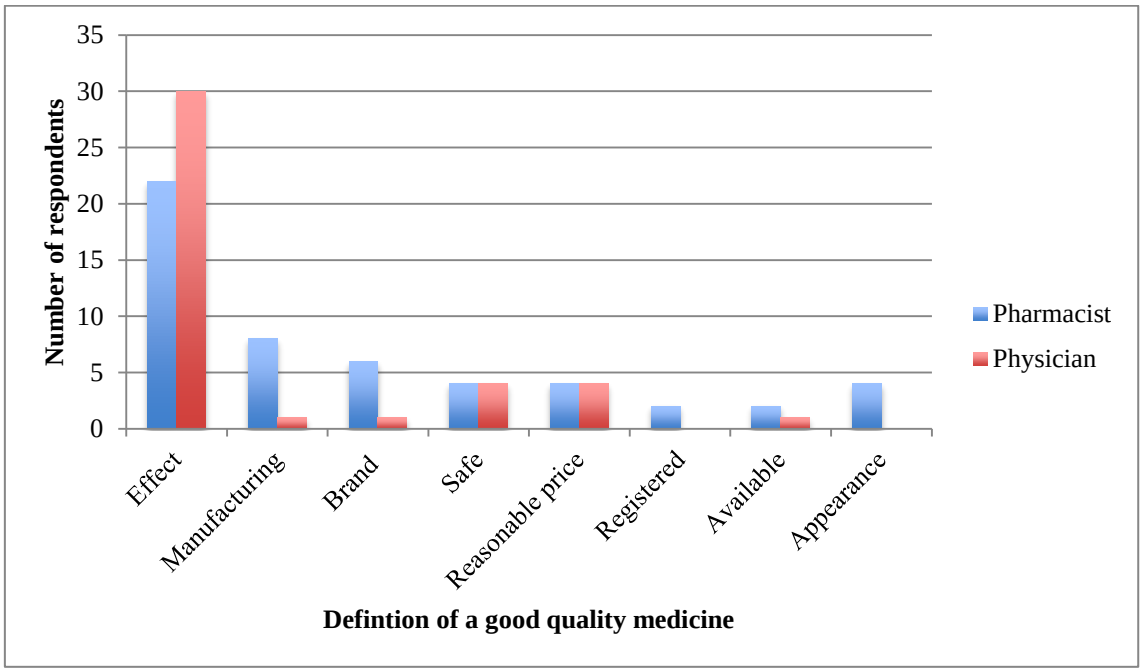


Figure 6.3 Definition of high quality medicine by pharmacists and physicians in the MOI-MSD

6.9.5.4 Medicine attributes of importance

Pharmacists and physicians were asked to rate the importance of 13 different medicine attributes on a scale from 1 to 10, where 10 was the most important. Both pharmacists and physicians believed that confidence in the medicine quality of production, SFDA registration, lot number and expiry date information, their personal experience with the medicine, clinical effectiveness and patient safety were important medicine attributes with an average score of more than 8 in both groups (Figure 6.4). Other medicine attributes such as manufacturing company details, patient information leaflet,

medicine's price, the experience of a friend or family member, medicine's availability and patient's preference were found to be of less importance according to the pharmacists and physicians' beliefs in this study, with an average score between 5 up to 8 on the rating scale (Figure 6.4).

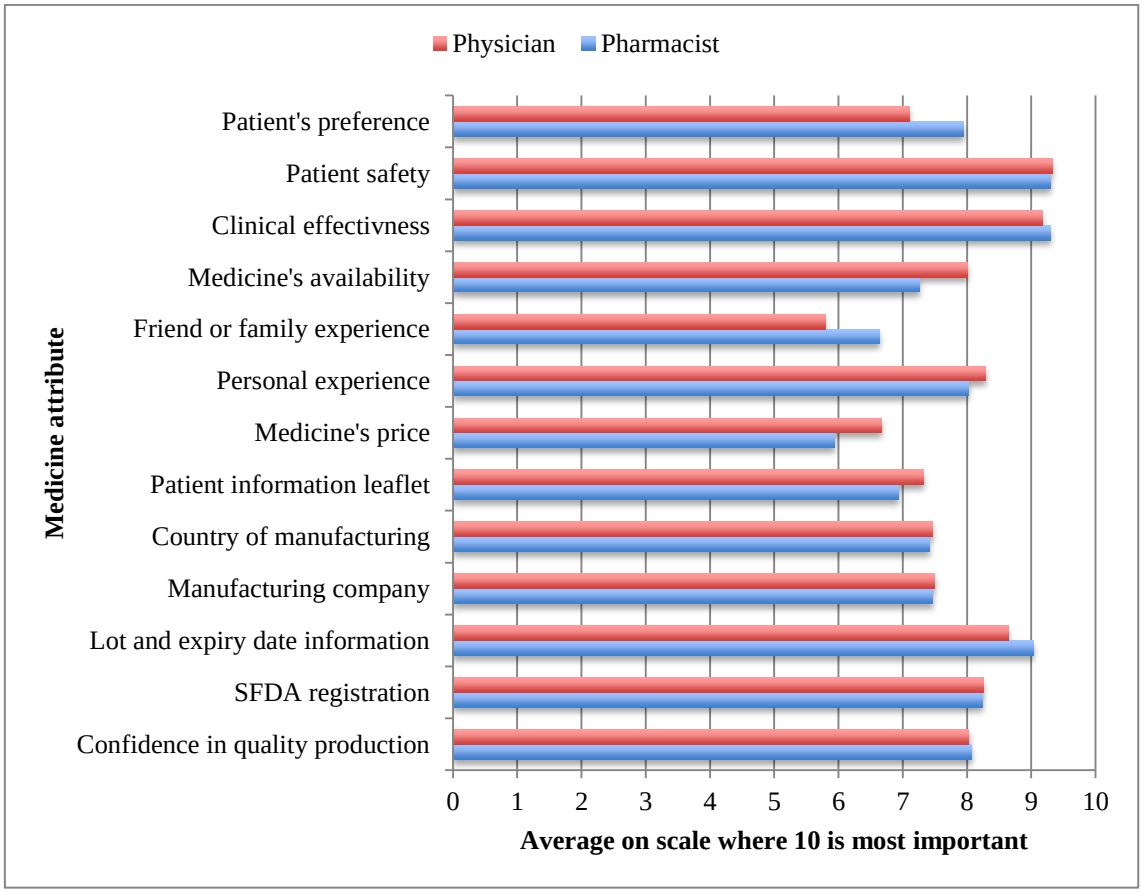


Figure 6.4 Pharmacists' and physicians' average rating on medicine attributes

6.9.5.5 Relationship between medicine price, health outcome and medicine quality

The pharmacist' and physicians' beliefs about the relationships between expensive medicines and medicine quality and health outcomes were examined on a scale from 1 to 10, where 10 was the most likely. On average, pharmacists were more likely to believe that expensive medicines resulted in a better medicine quality and better health outcomes, when compared with physicians in this study (Figure 6.5). In contrast, physicians rather than pharmacists were more likely to believe that medicine quality influenced their practice of prescribing on an average rating (Figure 6.5). Detailed

accounts for all pharmacists' and physicians' ratings on the relationships between medicine price, medicine quality, health outcomes and influence on practice can be found in (Figures 6.5, 6.6 and 6.7.)

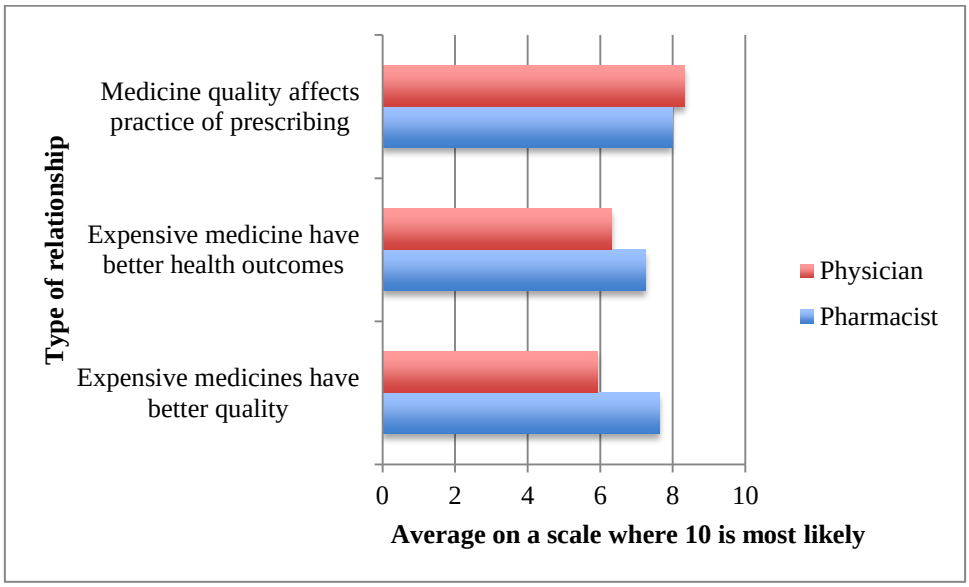


Figure 6.5 Price, health outcome, influence on practice and medicine quality relationships in physicians' and pharmacists' opinions

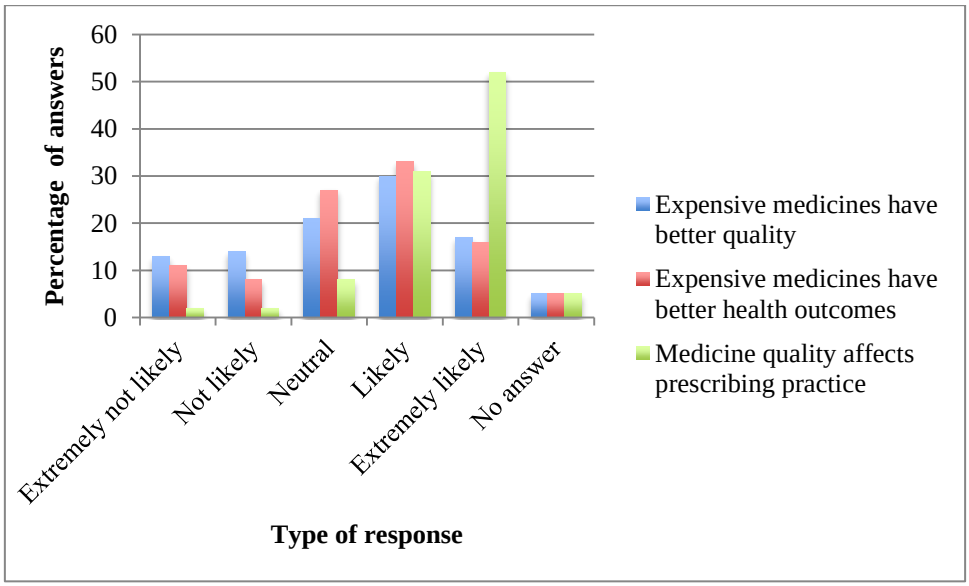


Figure 6.6 Price, health outcome, influence on practice and medicine quality relationships in physicians' opinions

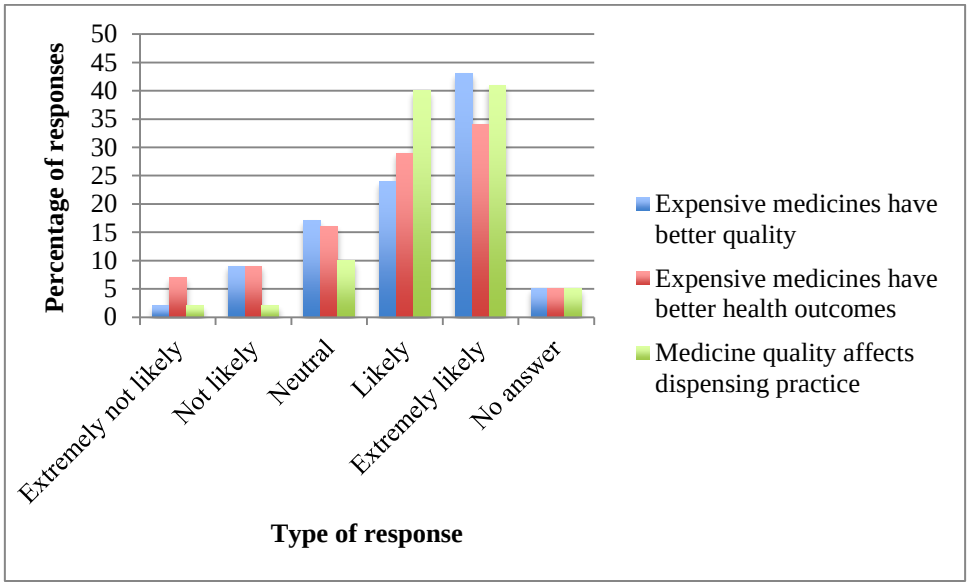


Figure 6.7 Price, health outcome, influence on practice and medicine quality relationships in pharmacist' opinions

6.9.5.6 Counterfeit medicines

Pharmacists and physicians were asked to define what a counterfeit medicine was. Some responses by the pharmacists (n=15, 26%) and most physicians (n=26, 41%) described a counterfeit medicine as one with minimal or harmful effect. Some pharmacists (n=6, 10%) and physicians (n=1, 2%) indicated that a counterfeit medicine has a manufacturing problem. Other characteristics of a counterfeit medicine were also described by the participants in this phase of the study such as no API, wrong API, wrong percentage of API, a medicine with an appearance problem, a fake copy of an original medicine, a medicine from an unreliable source or a non-registered medicine. Figure 6.8 lists all reported characteristics of a counterfeit medicine.

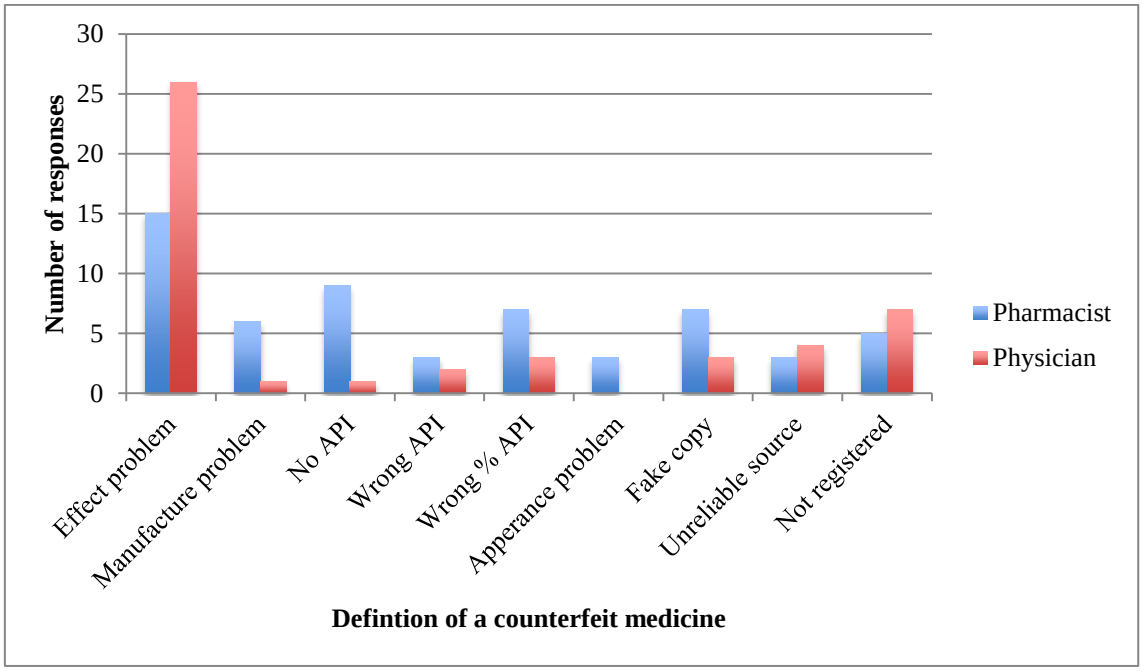


Figure 6.8 Definition of counterfeit medicines by pharmacists and physicians in the MOI-MSD

The majority of pharmacists and physicians in this phase of the study estimated that the global prevalence rate of counterfeit medicines was more than 10% of the pharmaceutical supply chain. Figure 6.9 illustrates all the respondents' estimations regarding the prevalence of counterfeit medicines globally.

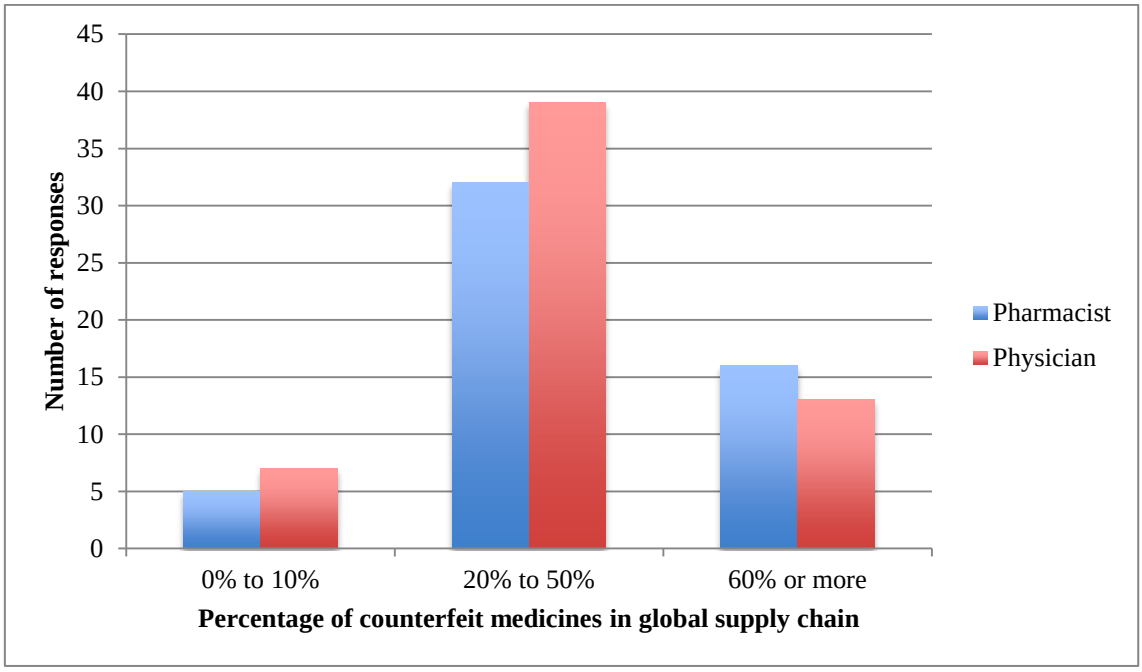


Figure 6.9 Pharmacists' and physicians' estimations about prevalence of counterfeit medicines globally

When asked about their estimation of the prevalence rate of counterfeit medicines in Saudi Arabia, mixed responses were obtained from both the pharmacists and physicians. Figure 6.10 contains a brief summary of the participants' estimations about the prevalence rate of counterfeit medicines in Saudi Arabia.

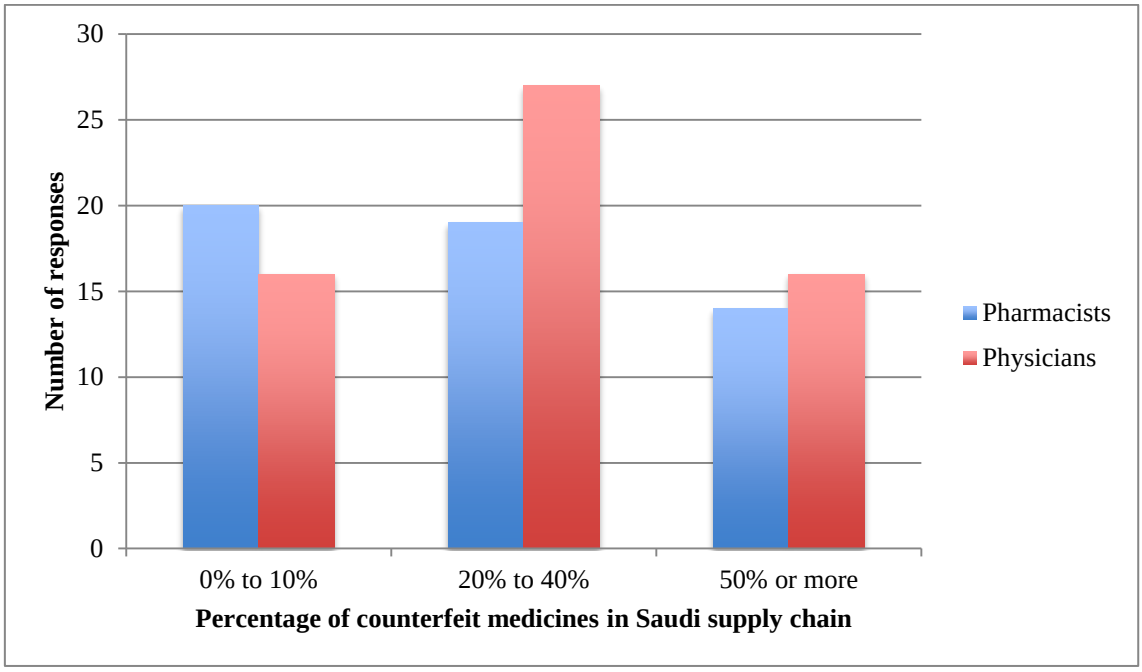


Figure 6.10 Pharmacists' and physicians' estimations about prevalence of counterfeit medicines in Saudi Arabia

6.9.5.7 Perception and behaviour regarding medicine quality and problems

On a scale from 1 to 10 where 10 is the best, the pharmacists (55%) and physicians (71%) in this study had the perception that medicine quality available in the Saudi Arabian market was above average in general. Both the pharmacists (50%) and physicians (52%) believed that medicine quality in their own settings at the MOI-MSD was lower than what is available in the Saudi Arabian market as a whole. Furthermore, pharmacists had lower rating scores for medicine quality in Saudi Arabia, in the MOI-MSD and in the medicines they dispensed on a scale from 1 to 10, where 10 was the best when compared to physicians (Figure 6.11). Detailed accounts for all pharmacists' and physicians' ratings on medicine quality in Saudi Arabia, the MOI-MSD and in the medicines they prescribed or dispensed can be found in Figure 6.12 and Figure 6.13.

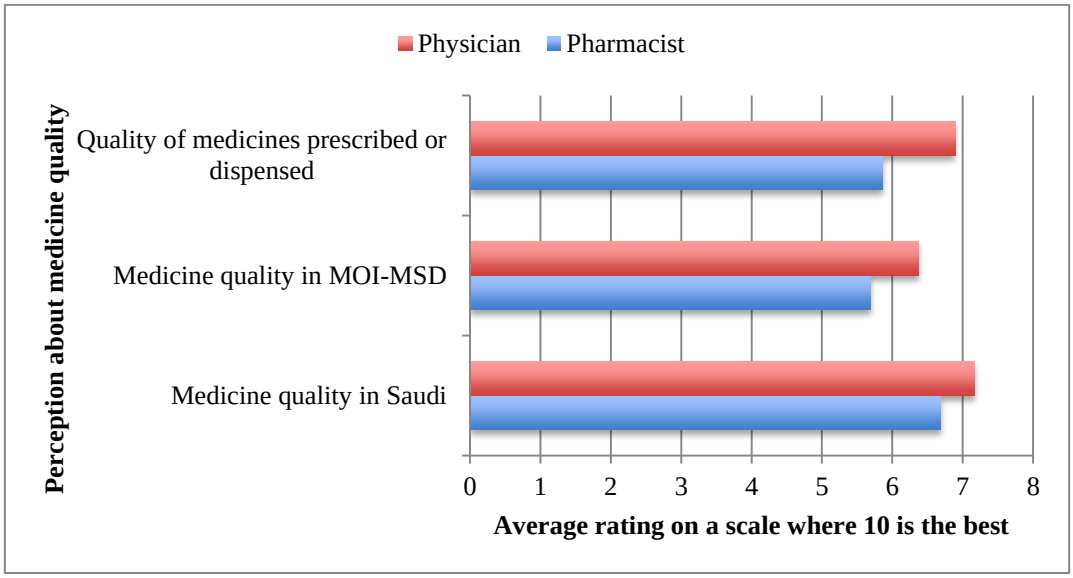


Figure 6.11 Pharmacists' and physicians' views about medicine quality in Saudi Arabia and the MOI-MSD

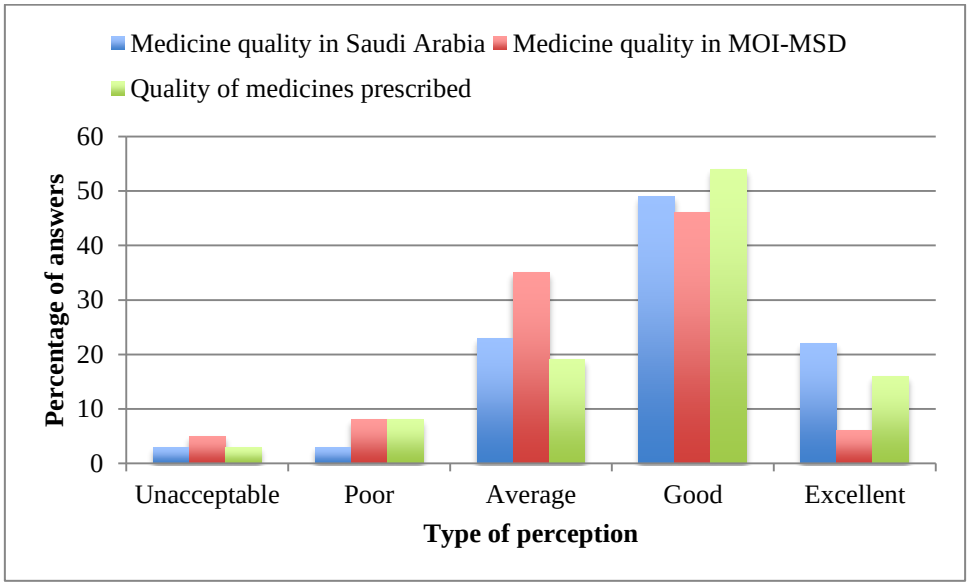


Figure 6.12 Physicians' views about medicine quality in Saudi Arabia and the MOI-MSD

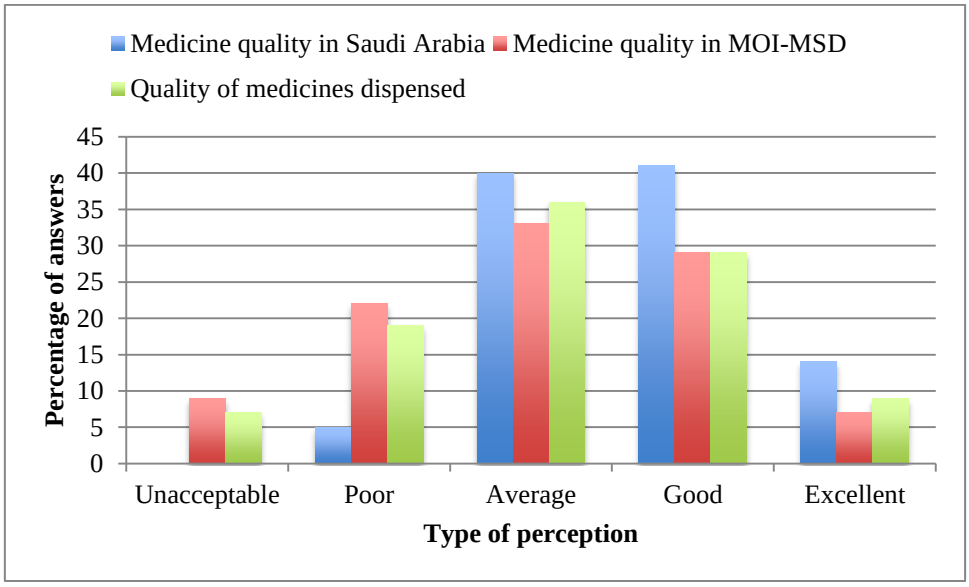


Figure 6.13 Pharmacists' views about medicine quality in Saudi Arabia and the MOI-MSD

Respondents were asked about the medicines therapeutic classes and formulations of concern in terms of quality. Both the pharmacists and physicians highlighted chronic disease and infectious disease medicines as the main therapeutic classes of medicine quality concerns. Furthermore, the pharmacists and physicians indicated that tablets and injections were the formulations of most quality concerns. Figures 6.14 and 6.15 illustrate all the physicians' and pharmacists' responses to identify therapeutic classes and formulations they thought were of most concern with regard to medicine quality.

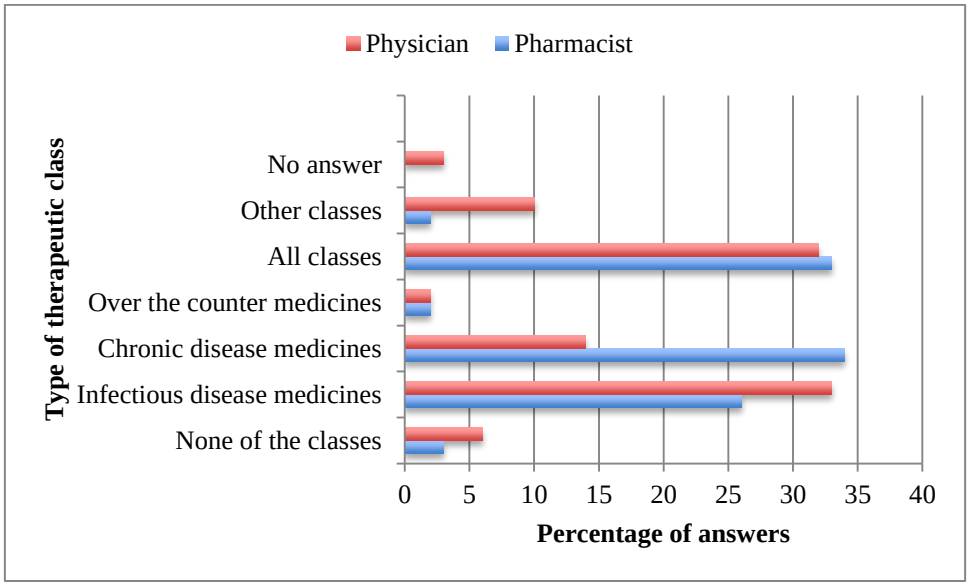


Figure 6.14 Therapeutic classes of concern to pharmacists and physicians regarding medicine quality

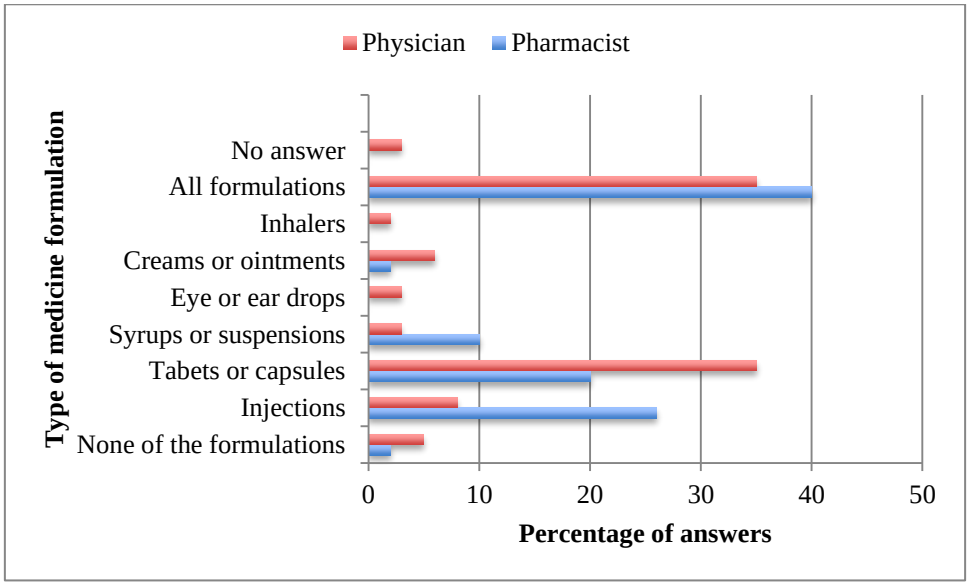


Figure 6.15 Medicine formulation of quality concerns to pharmacists and physicians

Some pharmacists (n=21, 36%) and physicians (n=13, 20%) reported experiences with medicines that had questionable quality within their practice in the MOI-MSD. The frequency of these encounters varied and can be found in Figure 6.16. When asked to describe these experiences, some descriptions were provided by the pharmacists and physicians in this study that can be summarised in Figures 6.17 and 6.18.

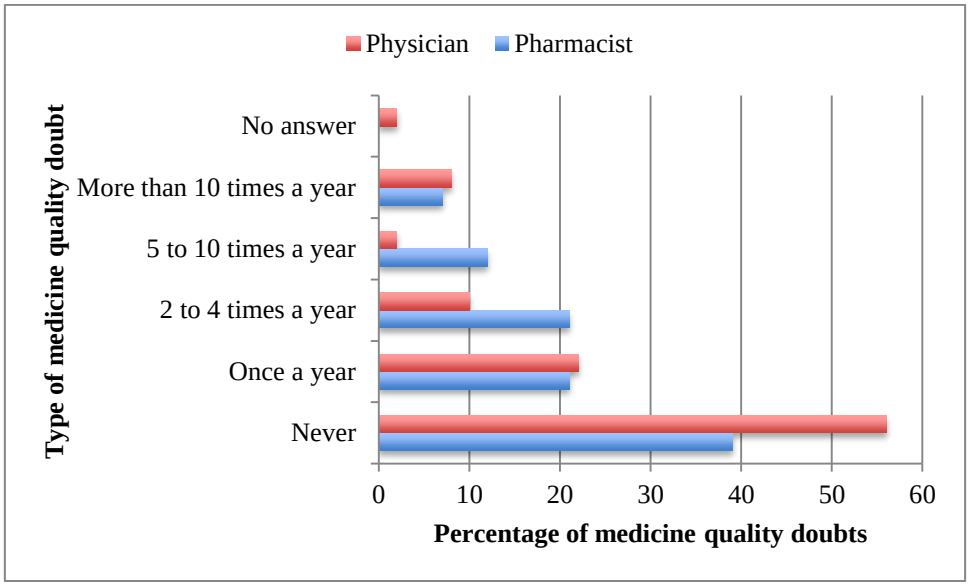


Figure 6.16 Frequency of pharmacists' and physicians' doubts about medicine quality in the MOI-MSD

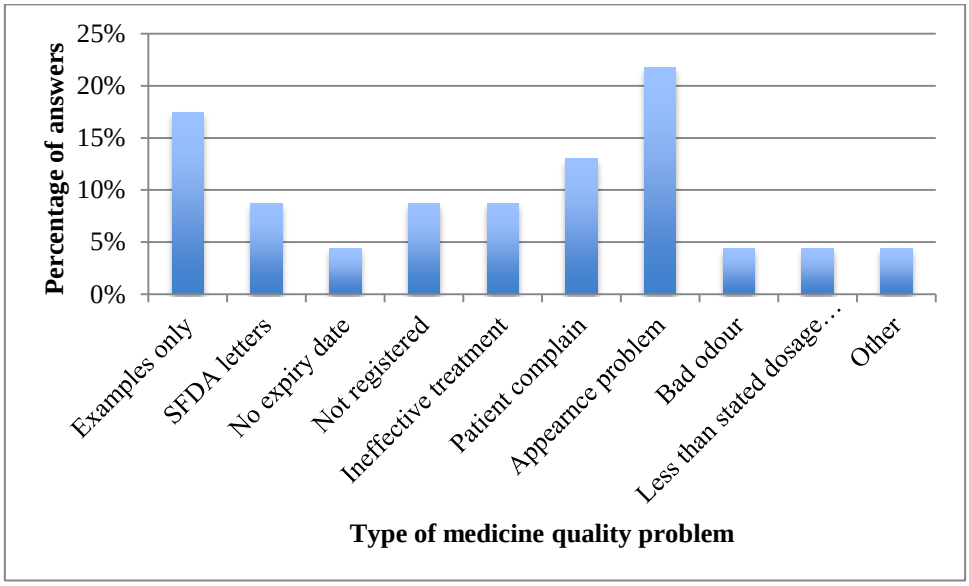


Figure 6.17 Pharmacists' encounters with medicine quality problems

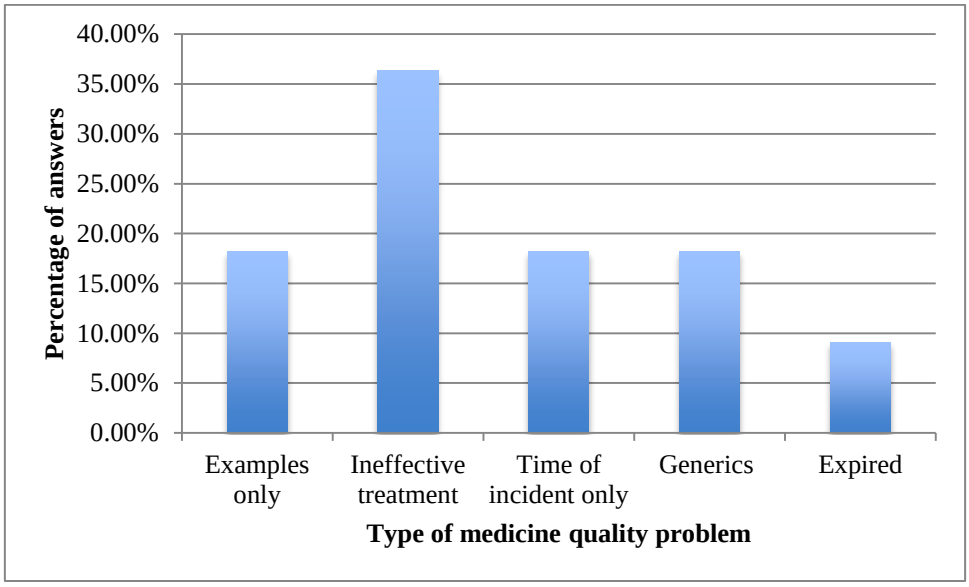


Figure 6.18 Physicians' encounters with medicine quality problems

The pharmacists and physicians were asked about their behaviour when in doubt about the quality of a medicine. The majority of pharmacists (n=35, 60%) and physicians (n=31, 49%) indicated that they reported it to the Director of Pharmacy. Some pharmacists (n=15, 26%) and physicians (n=35, 56%) highlighted that they took action by stopping dispensing or prescribing the medicine. A number of pharmacists (n=30, 52%) and physicians (n=14, 22%) considered reporting their doubts to the SFDA. Further details about the type of pharmacists' and physicians' behaviour reported when in doubt about the quality of medicines can be found in Figure 6.19.

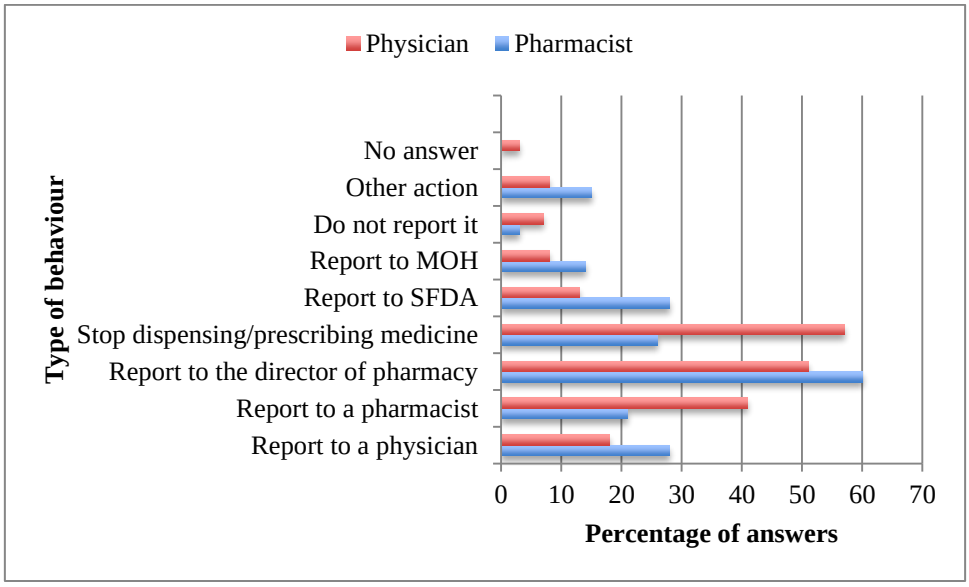


Figure 6.19 Pharmacists' and physicians' behaviour following doubts about medicine quality

*Multiple answers were allowed and hence percentages do not add up to 100%

6.9.5.8 Challenges to medicine quality and recommendations for improvement

Pharmacists and physicians were asked about their concerns about medicine issues at their settings in general, including quality. The most reported concerns were regarding medicine storage or transportation, medicine expiry dates, damaged medicine packages, patients' acceptance of the available medicines and the visual appearance of available medicines. Other less reported concerns included doubts about the presence of the correct amount of active ingredient. Figure 6.20 illustrates all the respondents' major concerns about medicines in this phase of the study.

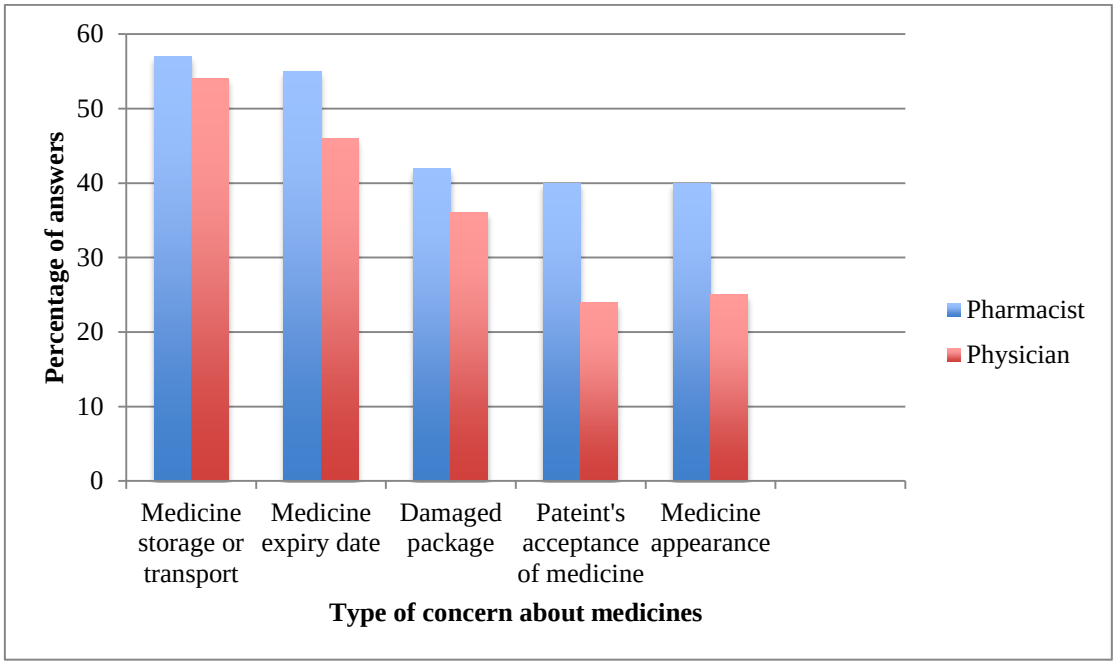


Figure 6.20 Healthcare providers' views on major challenges to medicine quality in the MOI-MSD

*Multiple answers were allowed and hence percentages do not add up to 100%

Pharmacists and physicians provided recommendations to enhance the medicine quality assurance in their settings. The majority of recommendations included the improvement of medicine practice at the warehouse and procurement level. Other recommendations were given at the Saudi Arabian regulatory and the MOI-MSD administrative level. Table 6.7 illustrates the recommendations of all pharmacists and physicians in this phase of the study.

Table 6.7 Pharmacists' and physicians' recommendations to enhance quality of medicines

Pharmacist (n=58)	Physicians (n=63)
No recommendation (12%)	**No recommendations (18%)**
At regulatory level (14%) More effort from SFDA (5%) Improve monitoring of medicines (3%) Strengthen registration process (1%) Analysis of medicine samples (5%)	**At regulatory level (18%)** More effort from SFDA (3%) Improve monitoring of medicines (9%) Analysis of medicine samples (6%)
At MOI-MSD administrative level (12%) Establish quality control section (8%) Establish policy and guidelines (4%)	**At MOI-MSD administrative level (8%)** Establish quality control section (3%) Establish policy and guidelines (5%)

At warehouse level (17%) Improve storage conditions (8%) Improve transport conditions (4%) Monitor expiry dates (1%) Visual check of medicine info. (4%) **At procurement level (17%)** Have more brand medicines (3%) Selection of medicines based on evidence and clinical experience (3%) Selection of medicines based on quality and less emphasis on price (5%) Buy from trustful suppliers or manufacturing companies (5%) Less procurement from tender systems (5%) **Increase education (4%)** **Improve communication with other healthcare organisations (4%)** **Staff to improve their practice in dispensing, preparation and prescribing (5%)** **Stop dispensing doubtful quality medicines (3%)** **Update the medicine formulary (1%)** **Establish a reporting system (1%)** **Conduct more research (1%)**	**At warehouse level (19%)** Improve storage conditions (10%) Improve transport conditions (6%) Monitor expiry dates (3%) **At procurement level (10%)** Have more brand medicines (4%) Selection of medicines based on quality and less emphasis on price (n=3%) Buy from trustful suppliers or manufacturing companies (3%) **Increase education (4%)** **Improve communication with pharmacists and staff (4%)** **Pharmacist to improve their practice and competency (3%)** **More control over OTC and antibiotics (1%)** **Classify drugs according to quality (1%)** **To have a good health information system (1%)** **To have good follow-up of cases and outcomes for patients (1%)**

6.9.5.9 Ordinal regression model

The independent variables explored in this model were the pharmacists' and physicians' perception about medicine quality in the MOI-MSD settings based on their rating scores from 1 to 10 where 10 is the best. The dependent variables included the pharmacists' and physicians' age, gender, education, region of practice and years of experience working in the MOI-MSD. The ordinal regression model fitting information was positive for both the physicians' and pharmacists' models and indicated that these models fit the data significantly (Table 6.8).

Table 6.8: Model fitting information table for pharmacists and physicians data

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Pharmacists	93.957	43.886	16	.000
Physicians	111.226	33.247	16	.007

In the pharmacists' data, the Goodness-of-Fit table had inconclusive results as shown in Table (6.9). While one test resulted in rejecting the null hypothesis and considering the model as inadequate (Pearson), the other test resulted in accepting the null hypothesis and considered the model as adequate (Deviance). In contrast, within the physicians' data, the Goodness-of-Fit table resulted in accepting the null hypothesis and considered the model as adequate.

Table 6.9: Goodness-of-Fit table for pharmacists and physicians data

Model	Test	Chi-Square	df	Sig.
Pharmacists	Pearson	145.695	16	.032
	Deviance	74.313	16	.999
Physicians	Pearson	119.012	188	1.000
	Deviance	99.796	188	1.000

The results of Wald's test in the parameter estimates table were mostly insignificant in the pharmacists' data except two variables (Age 50-59) and (Central region of practice). This would suggest that pharmacists' between the ages of 50 to 59 were three times more likely to have a poor perception about medicine quality in the MOI-MSD. It would also suggest that MOI-MSD pharmacists working in the central region in the country were 0.1 times more likely to have poor perceptions about medicine quality in their settings. Similarly, the results in the physicians' data were mostly insignificant except two variables (MSc education) and (having 1 to 4 years of experience in the MOI-MSD) as shown in Table 6.10. This would suggest that physicians with MSc education and also physicians with an experience between 1 to 4 years in the MOI-MSD were almost one time more likely to have a poor perception about medicine quality in their settings.

Table 6.10 Parameter estimate table for pharmacists and physicians

Model	Variable	Sig	OR	95% C. I. Upper	95% C. I. Lower
Pharmacists	Age 50-59	.000	3.04	12.650	26.567
	Central region of practice	.026	0.107	-4.190	-0.270
Physicians	Education MSc	.025	0.975	.250	3.645
	Experience between 1 to 4 years in the MOI-MSD	.015	0.985	.492	4.654

The test of parallel lines showed statistical significance for both the physicians' and pharmacists' models. This indicated that we have violated the assumption of the ordinal regression analysis and therefore caution is advised when interpreting the results (Table 6.11).

Table 6.11 Test of parallel lines for pharmacists and physicians

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Pharmacists	.000	93.957	48	.000
Physicians	.000	111.226	48	.000

Additionally, a Chi-Square statistical test was performed and found no statistical significance between the pharmacists' and physicians' perceptions about medicine quality in Saudi Arabia and the MOI-MSD as shown in Table 6.12.

Table 6.12 Chi-Square statistical significance between the MOI-MSD pharmacists' and physicians' perceptions about medicine quality

Characteristic	P-value
Perceptions about medicine quality in Saudi Arabia	0.950
Perceptions about medicine quality in the MOI-MSD	0.247

6.9.6 Discussion

The pharmacists and physicians in this study defined high quality medicines mostly through their perceived effects. This perception is in line with findings from other studies (Haddad et al., 1998; Syhakhang et al., 2004; Patel et al., 2009; Patel et al., 2010; Patel et al., 2012) conducted with patients and healthcare professionals in low and middle-income countries. However, findings from this study suggest that physicians (58%) associated medicine quality with medicine effects more frequently when compared with pharmacists (35%) in these settings. Pharmacists (24%) highlighted several medicine attributes such as manufacturing, source, expiry, storage and transport conditions to describe a high quality medicine compared to physicians (6%). This mirrors findings from other studies, for example, with nurses selling medicines in Laos (Syhakhang et al., 2004). Interestingly, few pharmacists (7%) and physicians (2%) used the term brand medicine to describe a high quality medicine, in line with similar studies (Syhakhang et al., 2004). In addition, pharmacists in this study held a stronger belief that more expensive medicines were associated with higher quality and better health outcomes when compared with physicians. These results are not without support from the existing literature (Tellis & Geath, 1990; Chapman & Wahlers, 1999; Syhakhang et al., 2004; Alfadl et al., 2012).

The respondents in this study had a perception that the quality of medicine was above average in Saudi Arabia. They believed that the quality of medicines in their own settings at the MOI-MSD was lower than what is available in the Saudi Arabian market as a whole. It is possible that the respondents were dubious about medicines procured from tender systems that could generally favour cheaper and alternative generic medicines, where possible. Further exploration using in-depth interviews with members of this population is needed to determine the factors associated with this belief.

Pharmacist in this study (59%) reported having doubts about medicine quality more frequently than physicians (44%). The experiences encountered by those reporting such doubts about medicine quality included not having an effect, expired, appearance problem, non-registration, bad odour, less than stated dosage quantity, patient complaints and information about product recalls issued by the SFDA. Moreover, their

practice when in doubt about medicine quality was mostly to report it to the Director of Pharmacy in their own settings. A total of 52% of pharmacists and only 22% of physicians have considered informing the SFDA of such doubts about medicine quality. This finding is alarming as it could hinder any efforts by the healthcare regulators in the country to collect and exchange information about suspicious medicines through pharmacovigilance programmes. Education and campaigns to facilitate nationwide reporting of medicine quality problems or suspicions are recommended in this population.

The notions pharmacist and physicians have about counterfeit medicines were explored in this study. Most physicians (45%) and some pharmacists (25%) defined a counterfeit medicine as one with no effect, minimal effect or with a harmful effect. This finding supports the medicine effect and quality perception discussed earlier. The majority of pharmacists' answers (48%) and some physicians (23%) described a counterfeit medicine as having problems in manufacturing, active ingredient, packaging, appearance and source. Only some pharmacists (13%) and physicians (7%) clearly specified that a counterfeit medicine was a fake copy of an original product that was intended for fraudulent deception. Similarly, only a few pharmacists (6%) and physicians (10%) defined a counterfeit medicine as unregistered or unauthorised by the SFDA. Interestingly, some physicians (4%) described a counterfeit medicine as one that has come from the Middle East. For the most part, the definition of counterfeit medicines provided by the respondents in this study does not reflect the WHO definition of counterfeit medicines which highlights the medicine identity, source, packaging and fraudulent activity as key features to determine a counterfeit medicine (WHO, 1999a).

The estimation of counterfeit medicines prevalence on a global scale was thought to be between 20% to 50% by most pharmacists (53%) and physicians (62%). Only 9% of pharmacists and 11% of physicians predict similar estimations to the WHO on a global scale at 10%. Also, 30% of pharmacists and 21% of physicians believed that counterfeit medicines contributed to 60% or more of the global pharmaceutical supply. The respondents' estimations of counterfeit medicines in Saudi Arabia were different. Most

pharmacists (38%) and some physicians (25%) agreed with the SFDA in that counterfeit medicine was non-existent or up to 10% of the Saudi Arabian market (Arabnews, 2010; Ameinfo, 2011). Further, 36% of pharmacists and 43% of physicians believed that it was between 20% to 40%, in line with local media reports in the country (Saudi Gazette, 2011). Moreover, 26% of pharmacists and 24% of physicians believed that the prevalence of counterfeit medicine in Saudi Arabia was 50% or more of the supply chain. It is possible that the limited understanding of what a counterfeit medicine was, which can be found in the literature (Jacobs, Coskun & Jedlik, 2001; Bosworth, 2006; Alfadl et al., 2012) and the results from this study could have contributed to such high estimations. There is a need for education about counterfeit medicine and strategies to enhance the healthcare professionals' confidence in the quality of medicines available in these settings, for better utilisation of the available medicine resources.

The majority of respondents believed that incorrect storage conditions, incorrect transport conditions and the presence of expired medicines were major challenges to medicine quality in these settings. Future observational studies could be employed to confirm or provide assurance for the concerned respondents. Some pharmacists and physicians had concerns about the presence and the correct percentages of the active ingredients in the available medicines. Chemical analysis tests on selected medicine samples from these settings could be performed according to international pharmacopeias in order to examine these concerns and to ensure that the results are widely published among the healthcare providers to support their knowledge in this regard. Interestingly, the results suggest that more pharmacists believed that patients' non-acceptance of their medicines was a challenge in these settings when compared with physicians. This could highlight the fact that the pharmacists are the last healthcare professionals in the supply chain facing patients when medications are supplied to them experiencing "non-acceptance" behaviour of patients first hand. Future in-depth interviews with this population could examine fully the reasons for such discrepancies and assumptions.

The pharmacists and physicians made several recommendations to enhance medicine quality in the MOI-MSD. The majority of recommendations included the improvement

of medicine practice at the warehouse and procurement level. Such recommendations could include improvement of the storage and transport conditions of medicines. In addition, more flexibility could be employed for the procurement of medicines through direct purchases in addition to tenders. However, such recommendations could be impractical particular with limited financial resources. Other recommendations were aimed at the Saudi Arabian regulatory and MOI-MSD administrative level to establish policy and guidelines, in addition to improving medicine monitoring in the country.

Implications for future research

This phase of the study has identified several areas that would require in-depth exploration using semi-structured interviews with a sample from the same sample frame. Firstly, it was unclear why some pharmacists and physicians in this phase of the study perceived a difference in medicine quality in the MOI-MSD and the medicines available in the Saudi Arabian market as a whole. Secondly, there were some negative comments regarding medicine procurement systems through tenders that required more understanding in terms of possible causes and recommendations to improve it. Thirdly, it was not clear how the participants in this study could make a clear judgment of whether a medicine was of good quality or not. Fourthly, difficulty in the reporting of suspected medicine quality problems has been noted from several comments made by the participants in response to open-ended questions and would require further exploration of those experiences and how to improve the reporting of such problems in these settings. Fifthly, it was found that physicians reported the behaviour of stopping prescribing a medicine with suspicious quality more often than pharmacist and, therefore, would require further insight for understanding the reasons for such differences. Furthermore, some medicine attributes were found to be of less importance than others in the opinions of the participants and therefore would require further exploration. Moreover, the participants made several recommendations that did not have sufficient details in order for them to be applied in these settings and hence the upcoming phase of this study is required to explore them in-depth.

Strengths and limitations of the survey questionnaire phase of the study

This present phase of the study had several limitations. The method of online self-

completed survey administration was less reliable than other forms of survey administration since the identity of respondents cannot be verified and the physical absence of the researcher does not allow for any further clarification of questions. The nature of most questions required predetermined answers; however, using the "other" option was frequently applied to allow for different opinions, to minimise the effect of framing bias. Some questions required answers from the respondents' past experiences and could be subject to recall bias. Moreover, some questions asked respondents about their practices regarding medicine quality issues and cannot be verified in the absence of an observational study. This survey has been designed and sent to members of the study sample frame and therefore findings are limited and cannot be extrapolated to other healthcare professionals within the same settings. Nevertheless, this study is among the very few studies that examined medicine quality issues from the perspective of different stakeholders. To the researcher's knowledge, it is the first study exploring such issues with pharmacists and physicians in Saudi Arabia and the MOI-MSD settings.

6.10 Phase 5: Confirmatory interview study of pharmacists' and physicians' survey questionnaire findings

6.10.1 Introduction

Research into medicine quality and their problems from the stakeholders' perspective is limited worldwide (Chapter 5). The perceptions about medicine quality and their problems have been previously explored from the different stakeholders' perspective including commissioners (Chapter 6 phase 2), patients (Chapter 6 phase 3) and pharmacists and physicians (Chapter 6 phase 4) within the MOI-MSD settings in Saudi Arabia in this study.

6.10.2 Aim

The aim of this phase of the study was to explore in-depth some issues regarding medicine quality found from the previous survey questionnaire phase of the study (Chapter 6 phase 4) with pharmacists and physicians in the MOI-MSD settings in Saudi Arabia in order to validate and supplement the survey findings.

6.10.3 Objectives

The objectives of this phase of the study includes the following:

- To explore in-depth the beliefs and views of pharmacists and physicians about medicine quality in the MOI-MSD
- Seek the pharmacists' and physicians' recommendations to improve the pharmacist's role, improve tender system for medicine procurement, improve reporting of medicine quality problems, quality assurance of medicines, medicine monitoring and analysis within the MOI-MSD
- Explore the perceived effect of some medicine attributes on the supply of medicine from the pharmacists' and physicians' perspective

6.10.4 Methods

In order to achieve the objectives of this phase, a qualitative approach using semi-structured interviews as a method for data collection was selected for flexible collection of data and achieved a greater in-depth understanding of this social phenomena (Smith, 2002; Morse & Field, 1995).

6.10.4.1 Selection of participants and study settings

The participants selected for this phase of the study were pharmacists and physicians working within the MOI-MSD settings. An invitation letter was sent from the Commissioner of Primary Care Clinics in the MOI-MSD on the researcher's behalf to all pharmacists and physicians working in MOI-MSD primary clinics electronically using WhatsApp smartphone application (Santa Clara, California USA; http://www.whatsapp.com). All MOI-MSD pharmacists and physicians had been previously sent a similar invitation during the previous survey phase of the study (Chapter 6 phase 4) and, therefore, an explanation was provided within the invitation letter that these interviews would complement the survey phase of the study on the same topic. The Commissioner of the primary care clinics provided the researcher with the contact details of potential participants who agreed to be interviewed. Telephone calls were made to ensure their agreement by verbal consent and to set up an appropriate time for the interview for each individual. A commissioner information sheet (Appendix 14), consent form (Appendix 16) and a demographic information sheet (Appendix 23) were sent via e-mail to all respondents who agreed to be interviewed.

6.10.4.2 Development of the interview guide

The semi-structured interview guide was developed based on the findings from the previous phases of the study (Chapter 6 phase 3) and (Chapter 6 phase 4). Table 6.13 highlights the key questions in the pharmacists' and physicians' interview guide.

Table 6.13 Pharmacists' and physicians' interview guide questions

1-In your opinion, what role does the pharmacist play in providing healthcare? How? Why? How can it be improved?
2-What do you think about the quality of medicines available in Saudi in general? In MOI? If different why?
3-What do you think about the tender system for medicine procurement? Why? How can it be improved?
4-How would you judge the quality of a medicine? Why?
5-What do you think about reporting of medicine quality problems? How? When? What happens after your report? How can it be improved?

6-What do you think about taking action (stop prescribing or stop dispensing a medicine) if you had doubt about its quality? Why?

7-How would country of manufacturing affect your supply of the medicine? Why?

8-How would the availability of a medicine affect your supply of the medicine? Why?

9-How would the experience of a family member or a friend with a medicine affect your supply of the medicine? Why?

10-How would price affect your supply of the medicine? Why?

11-How would patient preference affect your supply of the medicine? Why?

12-How would patient information leaflet affect your supply of the medicine? Why?

13-What do you think about the medicine storage conditions in MOI? How? Why? How can we improve it?

14-What do you think about the medicine transportation conditions in MOI? How? Why? How can we improve it?

15-What do you think about the patient acceptance of their medicines in MOI? How? Why? How can we improve it?

16-What do you think about the expired medicines in MOI? How? Why? How can we improve it?

17-What do you think about the monitoring of medicines in MOI? How? Why? How can we improve it?

18-What do you think about the analysis of medicines in MOI? How? Why? How can we improve it?

19-What do you think about establishing of a medicine quality section or department? How? Why? What level would be appropriate? What could it do?

20-What other recommendations do you have to ensure the supply of high quality medicines?

6.10.4.3 Validity and reliability checks

The validity and reliability checks were conducted in a similar method to the previous phases of the study (Chapter 6 phases 2 and 3). The interview guide was piloted with

two post-graduate Saudi Arabian pharmacists studying in the UH who were asked to provide feedback on the question content, order and clarity.

6.10.4.4 Data collection

All interviews were conducted via a telephone call with respondents in December 2014. The interviews were tape-recorded and conducted in the Arabic language, native to both the researcher and the respondents. The question order was similar for all participants to allow for data comparability where possible and to minimise the possible effects of variation of question order on the results (Patton, 1987; Alfadl, 2012). All interviews were conducted following the participant's signature of an informed consent form and none lasted longer than 50 minutes in this phase.

6.10.4.5 Questions and transcript translation

Interview guide questions were asked in Arabic in an attempt to maximise the participants' ability to express their thoughts freely. All participants were sent a copy of the interview transcripts via e-mail to ensure the accuracy of their statements and none proposed any changes. The validity of translation of questions and interview transcripts from Arabic to English was performed using a similar approach to previous phases of the study (Chapter 6 phases 2 and 3) using two random transcripts in the process.

6.10.4.6 Data analysis

Interview data were thematically analysed following transcription verbatim in Arabic and translation of data into English using the qualitative data analysis software NVivo, version 10 to generate major themes. The data analysis process followed a method adopted from Strauss & Corbin (1990) as previously discussed in other phases of the study (Chapter 6 phases 2 and 3). Coding and validation of coding were performed using a similar approach to previous phases of this study (Chapter 6 phases 2 and 3).

6.10.5 Results

6.10.5.1 Participant demographic characteristics

There were 16 participants who agreed to take part in this phase of the study, including 8 pharmacists and 8 physicians working in the MOI-MSD primary clinics. The characteristics of participants can be found in Table 6.14.

Table 6.14 Physicians' and pharmacists' demographic characteristics in the interview phase of the study

Category	Subcategory	Pharmacists (n=8)	Physicians (n=8)
Gender	Male	7 (88%)	8 (100%)
	Female	1 (12%)	0 (0%)
Age	20 – 29	1 (12%)	1 (12%)
	30-39	7 (88%)	3 (38%)
	40-49	0 (0%)	3 (38%)
	50-59	0 (0%)	1 (12%)
	60 or more	0 (0%)	0 (0%)
Education	BSc	3 (38%)	1 (12%)
	MSc	5 (62%)	1 (12%)
	PhD	0 (0%)	6 (75%)
Region of practice	Central region	5 (62%)	2 (25%)
	Western region	1 (12%)	5 (62%)
	Northern region	1 (12%)	0 (0%)
	Southern region	1 (12%)	1 (12%)
Years of experience working in MOI-MSD settings	Less than one year	0 (0%)	1 (12%)
	1 to 4 years	0 (0%)	0 (0%)
	5 to 9 years	5 (62%)	0 (0%)
	10 to 14 years	3 (38%)	4 (50%)
	15 years or more	0 (0%)	3 (38%)

6.10.5.2 Themes

Eight themes emerged from the pharmacists' and physicians' interviews as follows:

Theme one: Pharmacists' role in MOI-MSD primary clinics

The majority of participants (11/16) believed that the pharmacist's role was to educate the public, including other healthcare professionals, about their medicines. Several participants (7/16) held the opinion that the pharmacist's role was to dispense the correct medicine in the correct dose. Some participants (4/16) believed that the

pharmacist's role was comprehensive, starting from the medicine manufacture up to dispensing the medicine to patients. Other participants (4/16) specified the pharmacist's role as discovering medication errors.

"His importance in giving the correct doses to the patient, education to the patient, general medical advice, monitoring medicine movement in the body and raise awareness of the patient about the medicine" (Pharmacist 1)

There were other less common opinions about the pharmacist's role. A few participants (2/16) indicated that the pharmacist's role was to ensure proper logistic conditions for the medicines and a similar number of participants (2/16) highlighted the pharmacist's role in tracking the medicine movement in the body and in medicine formulation (2/16). Additionally, one participant believed that the pharmacist had a role in informatics coding of medicines and another participant reported that the pharmacist had a role in transferring the patient's feelings about the healthcare services to their administration.

"The pharmacist should be a checkpoint to convey the patients' feelings about the service…I mean managers don't know how the patient feels but they put plans that have results and we convey these results" (Pharmacist 6)

The participants in this phase of the study had several recommendations to improve the pharmacist's role within the MOI-MSD settings. Training and educational programmes aimed at the pharmacists in the MOI-MSD were suggested by half of the participants (8/16). Improving the communication between the pharmacists and other MOI-MSD staff, particularly physicians, was suggested by some participants (5/16). Some participants (3/16) suggested that a separate space should be allocated in each primary clinic for patient counselling. Other participants (3/16) believed that the pharmacist should have a more active role within the treatment team. There were some suggestions reported on an individual basis by the participants such as raising awareness about the comprehensive role the pharmacists play in healthcare, reviewing physician's prescriptions and improving patient education.

"…The doctor will make the decision regarding the disease but for treatment and management the pharmacist should support him...to increase the quality for people in specialties by sending some to study specific subjects that we need instead of just sending them all to study Pharm D" (Physician 6)

Theme two: Beliefs and views about medicine quality

The majority of participants (12/16) in this phase of the study believed that the quality of medicines manufactured in developing countries was inferior to the quality of medicines manufactured in developed countries. On a few occasions (2/16), it has been indicated that some patients held the belief that generic medicines were inferior to brand medicines but this view was not shared by the healthcare professionals.

"…When you take it from some companies and unfortunately they are local companies and take medicines from foreign companies you notice the difference in medicine results and effect…" (Pharmacist 4)

Nearly half of the participants (7/16) described the quality of medicines in Saudi Arabia as excellent. Some (5/16) believed that it was average: that some medicines were of good quality and others were not. Only one participant described the quality of medicines in Saudi Arabia as poor and another participant did not know what the quality of medicine in the country was. One participant suggested that the quality of medicines has recently improved in the country. Moreover, half of the participants (8/16) in this phase of the study believed that the quality of medicines in the MOI-MSD was similar to the quality of medicines in Saudi Arabia as a whole. Some participants (3/16) explained these views by stating that the quality of medicines is similar to what is available in the local market because they are all supplied from the same source.

"MOI-MSD is part of the healthcare services in Saudi Arabia so we have the same medicines to some extent" (Pharmacist 1)

Several participants (5/16) believed that the quality of medicines in the MOI-MSD was less than what is available in the Saudi Arabian market. Others (4/16) indicated that the

medicine quality available to them was less than the quality of medicines available in other Saudi Arabian hospitals including the MOI hospital. A few participants disagreed with these views by indicating that the medicine quality is now improving within the MOI-MSD (2/16) and that the quality of medicines in the MOI-MSD was better than what is available in the Saudi Arabian market (1/16). One participant held the opinion that the quality of medicines in the MOI-MSD was average: that there are medicines of good quality and others that are not. There were several reasons provided by the participants to explain why they thought the quality of medicines in the MOI-MSD was different from what is available elsewhere in Saudi Arabia. Some participants (4/16) indicated that it would be a result of the difference in tenders and medicine prices. Others (4/16) indicated that the difference is in the medicine manufacturers used. A few participants (3/16) believed that it is a result of outdated medicines available in the MOI-MSD formulary. One participant held the opinion that medicines in the MOI-MSD receive more attention than other healthcare providers such as the MOH. Furthermore, one participant believed that the difference in medicine quality could be attributed to the lack of efforts to improve medicine quality in the MOI-MSD settings.

"I think there is a difference in financial abilities between hospitals in Saudi where there are hospitals with excellent financial abilities who have excellent medicines and that is why the patients like to be treated there because their medicines are good"

(Physician 4)

When the participants were asked how they determined the quality of medicines, a number of methods have been suggested. The majority of participants (12/16) involved the patient at the centre of their answers, particularly from the physician's group (8/8). The quality of medicines could be determined by the patient's reported effect (4/16), their acceptance of a medicine (5/16) and the degree of their compliance with the medicine (1/16). The patient experience with the medicine quality of any product could be achieved through the physician's follow-up with the patient (4/16) and the pharmacist's questions about their previous use of a medicine (2/16). Other reported methods for determining the quality of a medicine included laboratory analysis of medicine samples (4/16) and visual checks of the medicine appearance (2/16), particularly from the pharmacist group (5/8). Published research articles have been

identified as a method to determine medicine quality (5/16) particularly from the physician's group (4/8). Furthermore, the medicine manufacturers' reputation (3/16) and the physicians' experience from treating multiple patients (2/16) have also been identified as a method to determine the quality of a medicine exclusively by members from the physician's group.

Theme three: The tender system for medicine procurement

Most participants (10/16) in this phase of the study stated that they do not have sufficient information about the tender system used for medicine procurement in the MOI-MSD. However, some (7/16) believed that it focused on the cheapest prices. Others (4/16) believed that it does not focus on the quality of medicine manufacturing. There were a few (3/16) participants who clearly stated that they were unhappy with the current tender system for medicine procurement within the MOI-MSD. There were some justifications provided by participants for their dissatisfaction with the current medicine procurement system, including their view that it would not be appropriate for medicine (2/16), that it would result in frequent changes to the available medicine trade names (2/16) and it would result in receiving medicines that were different from the medicinal products that have been experienced and studied in the literature (1/16).

"The idea of governmental tenders where you buy the cheapest would be suitable if you were buying cars, typewriters or offices but not medicines … because you took the cheapest so you will settle for less. When they take the medicine because it is cheapest, it is cheaper but also worse" (Pharmacist 6)

"…Most patients have a psychological factor for example if glibenclamide changed from one company to another or to the brand, so every change in 3 months in procurement causes problems with the patients when you try to convince them that it is the same medicine as the first one…" (Pharmacist 8)

Several recommendations have been made by the participants to improve the current medicine procurement practice. Involving staff from different MOI-MSD departments in the medicine procurement process has been suggested by some (6/16). Finding other alternatives to the current tender system has been suggested by others (2/16). There

were other individual suggestions, such as procuring the same medicines for chronic patients, unifying the medicines available in MOI-MSD primary clinics and hospitals, conducting bioequivalence studies on all generic medicines, adding a quality criterion in the medicine selection process at tenders, learning from other Saudi Arabian healthcare providers' experiences in medicine supply and to conduct cross-sectional studies about medicine quality and their problems in MOI-MSD settings and report their findings.

"There should be a medical committee consisting of physicians and pharmacists who based on their experiences would know specific medicines that would be suitable regardless of the price because quality is more important than price" (Physician 5)

Theme four: Reporting of medicine quality problems

Several participants (5/16) believed that the reporting of medicine quality issues was an important subject. However, nearly half of the participants (7/16) held the opinion that reporting medicine quality problems was not active in the MOI-MSD and requires further improvements. Other limitations of the current situation of medicine quality problem reporting were also mentioned, such as not having a clear mechanism or responsible personnel for the collection of such data (4/16) and being currently performed manually using paper-based documents (4/16). Furthermore, other barriers to the reporting of medicine quality problems were also highlighted on an individual basis such as patients underreporting such problems, inability to find reporting forms, lack of incentives to the reporter and that reporting of such problems might be unnecessarily problematic for the reporter.

"…If someone reports a medicine or bad things about a medicine then you will get questioned … you won't get even a thank you…. Therefore, many pharmacists do not care about this issue …" (Pharmacist 5)

The participants in this phase of the study provided several recommendations to improve the reporting of medicine quality problems within the MOI-MSD. Most participants (10/16) believed that it would be necessary to establish a department or a committee to collect data about medicine quality problems. Other suggestions included

improving education about medicine quality problems (3/16), encouraging staff to report such problems by providing incentives (3/16), establishing an electronic reporting system (2/16), establishing patient counselling in pharmacies (1/16) and expressing appreciation for any suspected quality problem report, even if proven inaccurate (1/16).

"There should be a committee that receives the reports of medicine complications or problems … and then this committee would report it to the SFDA…" (Physician 2)

Theme five: Storage and transportation of medicines in the MOI-MSD

The participants' views about medicine storage within the MOI-MSD had mixed responses. Some believed they were good (3/16), others believed they were poor (2/16) and some (5/16) did not know what the storage conditions were. However, some participants (6/16), particularly from the physician group (5/8), indicated that the ideal storage conditions in the main store in Riyadh were different from the poor storage conditions in other MOI-MSD primary clinics.

"I don't know about Riyadh, but here in the primary clinic it is very poor. There isn't appropriate temperature or air-conditioners supply and the location too, it used to be in the basement where you would even find cats and mice with the medicines…" (Physician 2)

Several recommendations for improving storage condition in the MOI-MSD settings were provided by the participants. Some participants (5/16) suggested establishing new warehouses that are up to international standards. Others (3/16) suggested embracing technology such as the use of robots, forklift trucks and electronic shelves in order to facilitate medicine storage. Other less frequent suggestions included establishing a department to monitor medicine storage (2/16) and establishing one new main warehouse in each region of the country.

The participants' opinion on medicine transportation within the MOI-MSD also displayed mixed views. Some (6/16) believed the transport conditions were poor, particularly within the pharmacist group (5/8). Others (4/16) believed that the medicine

transportation conditions were good. There were some physicians who did not know what the medicine transportation conditions were (4/16). The main participants' concerns about medicine transportation in these settings were that medicines were commonly transported in open-trunk cars (4/16) and therefore might be exposed to extreme weather conditions in the process (6/16).

"This is the worst side of MOI-MSD … In the MOH, it is prohibited to transport medicines in open trunk cars. Unfortunately, we only have one or two cars that are specialist in medicine transportation…" (Pharmacist 5)

Several recommendations were offered by the participants in order to improve the medicine transport conditions in the MOI-MSD. Transportation of medicines via airplane to distant primary clinics has been suggested (3/16). Others suggested that medicines could be distributed by a specialised distribution company (3/16) or adequately refrigerated cars (3/16). It has also been suggested to include thermometers with each medicine consignment distributed (2/16) and to establish a department to monitor distribution (2/16). Other individual recommendations included training of personnel responsible for medicine transportation and direct delivery of medicines from the supplier to regional primary clinics without the involvement of the general warehouse located in Riyadh.

The issue of expired medicines within the MOI-MSD produced different views from the participants. Some (7/16) believed that it was a problem in these settings particularly within the physician's group (5/8). Others (6/16) believed that it was not a problem particularly within the pharmacist's group (4/8). Furthermore, some participants (7/16) raised an issue with nearly expired medicines that were delivered to MOI-MSD primary clinics as a challenge in these settings.

"There is a problem here with the nearly expired here…they are not expired because I don't think someone would receive expired medicines…" (Pharmacist 2)

Several recommendations have been proposed by the participants to address the issue of expired medicines in the MOI-MSD settings. Such recommendations included the collection of statistical data regarding the quantity of dispensed medications from all primary clinics (5/16), establishing a department to monitor expired medicines (4/16), use of computers in warehouses to dispense near expiry medicines first (4/16), medicine suppliers to deliver medicines with a minimum acceptable expiry date (3/16) and encouraging primary clinics to exchange nearly expired medicines between each other and with other healthcare organisations (3/16).

"I think it needs precise calculations…Communicating through the system would be better to ask for exchange with colleagues…" (Pharmacist 6)

Theme six: Patients' acceptance of available medicines in MOI-MSD

The participants expressed different opinions regarding the patient's acceptance of their medicines in the MOI-MSD primary clinics. Some (7/16) believed that the patients did accept their medicines in these settings. Others (3/16) believed that they mostly accepted their medicines but with some issues on occasions. Furthermore, only a few participants (3/16) believed that patients had poor acceptance of their medicines in these setting. The most common barriers to patient acceptance of their medicines have been identified by some participants, including that some patients demanded brand medicines (5/16) and some patients preferred to have similar medicines to those available within the MOI-MSD hospitals (2/16).

"Sometimes there are certain issues… if there were specific brand names other than what I give him and he tried them and was comfortable with them… in this situation I don't try to talk to him. I would only talk to a patient if I saw something that has harm... I think it is his right to take the brand and I support him in that" (Physician 1)

The participants provided some suggestions to improve the patients' acceptance of their medicines. Improvement of medicine supply and selection has been suggested by several (7/16) participants. Staff reassurance about the quality of the medicines available in the MOI-MSD has been highlighted by a few (3/16) participants. Other

suggestions included patient education about their medicines (2/16) and supplying the same medicines as the MOI-MSD hospital (2/16).

"I myself need to be sure that this medicine is the same as the other medicine before I talk…I don't want to tell a patient that this medicine is similar to the other and then two months later a report is written about it. This would make my image not look good and I would have betrayed the patient in all honesty" (Pharmacist 6)

Theme seven: Recommendations to enhance quality assurance

The medicine monitoring issue has been perceived by some participants as excellent in the MOI-MSD (2/16) and as currently improving by others (3/16). However, there were some participants (3/16) who believed that medicine monitoring does not exist in the MOI-MSD and one participant who did not have sufficient knowledge about medicine monitoring in these settings.

When asked about what medicine monitoring means in their opinion, some participants (4/16) believed that it means a comprehensive monitoring of medicines from the point of storage in the warehouse until the patient uses them. Other participants (4/16) specified monitoring medicines during storage and dispensing. A few participants (3/16) specified monitoring medicines during dispensing in order to adequately forecast future required quantities of different medicines.

"…The monitoring from the warehouse to the pharmacy. The monitoring of quantities, expiry dates and dispensing…" (Physician 2)

Several recommendations were provided in order to improve medicine monitoring. The establishment of a department or a committee to monitor and collect data about medicines has been suggested by nearly half of the participants (7/16). Other suggestions included the use of existing electronic systems to monitor medicines in all primary clinics (1/16), education and training of staff (1/16), in addition to the use of barcode technology to enable medicine monitoring.

Although the issue of medicine analysis has been perceived as an important issue by some participants (4/16), nearly half of the participants (7/16), particularly pharmacists (5/8), believed that it is essentially the responsibility of the SFDA and not the MOI-MSD. The only role that the MOI-MSD staff can perform regarding medicine analysis is to actively send medicine samples to the SFDA and wait for analysis results, according to some opinions (3/16). It appears that a common belief among some participants (7/16) is that conducting medicine analysis within MOI-MSD settings would be wasteful of resources and staff efforts.

"…You shouldn't do someone else's job, which is the SFDA and medical licenses…" (Pharmacist 8)

Various suggestions to improve medicine analysis in the MOI-MSD settings have been proposed by participants. Such suggestions included requesting information regarding medicine analysis results and the registration status of medicines from the SFDA (2/16), encouraging the SFDA to send the MOI-MSD copies of medicine analysis results (2/16), establishing one SFDA analytical laboratory in each region of the country (1/16), routine and periodic collection of medicine samples to be sent to the SFDA for analysis (1/16) and for medicine suppliers to include an analysis certificate of each delivered batch of medicines to the MOI-MSD (1/16).

The majority of participants in this phase of the study (14/16) believed that the establishment of a medicine quality department within the MOI-MSD settings would be important. They believed that the establishment of such a department would be helpful in the protection of public health (1/16), protect medicines which are the bases of MOI-MSD medical services provided to patients (2/16) and would assist primary clinic pharmacists to focus on their daily work (2/16).

"…I think it is important to have a section for medicine quality in MOI-MSD because medicine safety is very important … I know in the National Guard and the Defense Ministry, they do have a department for medicine quality" (Pharmacist 1)

There were a number of recommendations provided by the participants in order to achieve the best possible outcomes by establishing a medicine quality department in these settings. More than half of the participants (9/16) believed that this department should be located in the MOI-MSD headquarters and that it should have representatives in all primary care clinics (5/16). Other suggestions included having a sufficient number of staff in this department (4/16), with adequate training on the subject (2/16) and using electronic means of communication between the department and the stakeholders (3/16).

The participants have also expressed their thoughts on the potential roles that this department could contribute to the MOI-MSD healthcare services. The majority of participants (10/16) held the opinion that this department could monitor medicine quality throughout all stages of the medicine cycle from the point of receiving the medicines in the warehouse until it is dispensed to the patient, particularly within the pharmacist group (6/8). The medicine quality department could also be responsible for conducting research on patient satisfaction and patient response to their medicines, according to some opinions (6/16). It could also act as a link between the SFDA and different stakeholders within the MOI-MSD regarding medicine quality problems in order to facilitate rapid information exchange (6/16). Furthermore, the medicine quality department could adopt an educational role by educating MOI-MSD staff about medicine quality problems according to the latest research worldwide (4/16).

Theme eight: Medicine attributes affecting medicine supply

The medicine country of manufacture was perceived as an important factor in the supply of medicines by half of the participants (8/16) particularly from within the pharmacist group (6/8). Other participants believed that it was not important (3/16), could be important on some occasion (2/16) or had no opinion on this topic (2/16).

The participants had several reasons for considering country of manufacture as an important attribute in medicine supply. Different countries were perceived as having different medicine monitoring abilities (2/16), different reputations regarding the quality of their medicines (2/16) and different economic ability to ensure the safety of their

medicines (2/16). Furthermore, it has been suggested that importing medicines from distant countries could result in medicine shortages (2/16) and that political relations between two countries could be associated with the inability to supply medicines from pharmaceutical manufacturers in certain countries (2/16).

"Medicines manufactured in America … are different than the medicines manufactured in Arabic countries…the manufacturing material, monitoring and reputation"
(Pharmacist 5)

The majority of participants (11/16) believed that medicine availability is an important factor in medicine supply. Other participants believed that the impact of medicine availability on medicine supply was either not important (1/16), occasionally important (2/16) or had no opinion on the subject (2/16).

Most participants considered medicines that are readily available to be preferred by both the healthcare providers and patients (6/16), and that medicines that are not available in the market could raise suspicions about the reasons for their non-availability (2/16). Furthermore, the participants believed that a medicine's non-availability could cause several undesired outcomes such as inability of primary clinics to provide any services to patients (1/16), patient non-compliance (1/16), deterioration in a patient's health condition (1/16) and the patient taking the wrong alternative medicine (1/16).

"…This would affect the compliance of the patient, create complications and maybe cause deterioration or morbidity and mortality increases…" (Physician 6)

Most participants did not consider the experience of a friend or a family member important in medicine supply (10/16). Some participants believed it was important (2/16), occasionally important (3/16) or had no answer (1/16).

The participants justified their common belief about the insignificance of a family or friend member experience in medicine supply by indicating that such experiences were not based on sufficient evidence to be considered in supply decisions (5/16), patients

reacted differently to the same medicine (4/16), not all patients preferred the same medicine (2/16) and that supply decisions should be made by a professional committee within MOI-MSD settings (2/16).

"…Experience of a friend or a family member is not evidence based for us to depend on to supply the medicine because for sure there is much variability between patients"
(Physician 8)

More than half of the participants (9/16) considered medicine price as an important attribute in the medicine supply decision. Other participants believed that medicine price was not important (4/16), sometimes important (2/16) or had no opinion regarding this topic (1/16).

There was a common belief (4/16) that expensive medicine prices have resulted in patients' acceptance of lesser quality and cheaper medicines, particularly from within the physicians' group (4/8). Furthermore, some participants (2/16) suggested that higher medicine prices guaranteed a higher quality medicine. It has also been suggested that medicine price is an important attribute since it is highly emphasised in the governmental procurement tender systems (1/16).

The impact of patient preference on the medicine supply decision had mixed responses from the participants in this phase of the study. Some believed it was important (3/16) or possibly important (3/16). Others did not believe it was important (6/16), particularly from within the physicians' group (4/8), or had no opinion on the subject (4/16).

The participants who believed that patient preference was important or possibly important in medicine supply justified their views by indicating that patients would not take their medicines if they were supplied without considering their preference (4/16) and that ethical issues may arise with the patient's right to choose the medicines that they will take (1/16). In contrast, the participants who did not believe that patient preference would be important in the medicine supply decision have highlighted that patient preference would not make a difference in deciding which medicines were

available within the MOI-MSD (2/16) and that it would be impossible to please all patients (3/16).

The participants had also mixed responses about the significance of the medicine information leaflet on the medicine supply decision. Some participants believed that it was important (5/16) or possibly important (2/16). Others held the opinion that it was not important (5/16) or did not have an answer (3/16).

The participants who believed that the medicine information leaflet was important in the supply decision have indicated that the patient has the right to know everything about their medicine (3/16) and that the absence of the medicine leaflet would raise suspicion about the medicine (1/6). In contrast, the argument of views that did not consider that the medicine information leaflet important in the supply decision, involved reasons such as most patients do not read them (2/16), being scientifically invalid or bias towards the manufacturer (2/16), it includes unnecessary information about rare side effects (2/16) and is written in small font size that complicates the process of reading it (1/16).

6.10.6 Discussion

Most participants in this phase of the study perceived that the pharmacist's role in MOI-MSD settings is mainly as a provider of medicine-related information. Studies conducted in neighbouring Arab countries such as Kuwait, Jordan, Qatar and Iraq have shown that physicians perceive pharmacists as a reliable source of information regarding medicines (Matowe et al., 2006; Tahaineh, Wazaify, Albsoul-Younes, Khader & Zaidan, 2009; Zaidan, Singh, Wazaify & Tahaineh, 2011; Hamadi, Mohammed, Dizaye & Basheti, 2015). Nearly half of the participants perceived that the pharmacist's role is as a medicine dispenser in these settings. This opinion is in line with the more traditional view of the role of pharmacists in the compounding and dispensing of medicines (Jones, Mackinnon & Tsuyuki, 2005). However, only one quarter of participants in this phase of the study recognised that a pharmacist can detect medication errors and be part of the medicine cycle, starting from medicine manufacture right through to medicine administration. Furthermore, the participants have suggested increasing pharmacists' training and education, improving pharmacists' communication skills and conducting patient counselling as key components in order to improve the

pharmacists' role in the MOI-MSD settings.

A large number of participants in this phase of the study believed that the quality of medicines manufactured in developed countries was better than the quality of medicines manufactured in developing countries. These views are in agreement with and could explain finding from previous phases of this study within the commissioner's group (Chapter 6 phase 2) and the healthcare provider's group (Chapter 6 phase 4), where a common belief was reported that medicines with higher prices, most likely imported from developing countries, were considered to be of better quality.

Most participants had mixed views about the quality of medicines in Saudi Arabia, ranging from excellent to average. These results were similar to reports from all stakeholders in this study. Half of the participants believed that the quality of medicines in the MOI-MSD was similar to that available in the Saudi Arabian market, because the medicines are supplied from the same source. However, less than half of the participants believed that the quality of medicines in the MOI-MSD was less than that available in the Saudi Arabian market because of different tenders used to supply medicines in different healthcare sectors in the country, different manufacturers used to supply the medicines and outdated medicines available in the MOI-MSD medicine formulary.

The majority of participants in this phase of the study used information related to patients in order to make a judgment about the quality of a medicine. Such information included patient's reported effect and experience with the medicine used, patient's acceptance of the medicine and patient's compliance with the treatment regimen. This finding was in contrast with the current technical nature of determining medicine quality through laboratory testing according to pharmacopoeial specifications (Patel et al., 2010). Only one quarter of the participants referred back to the scientific literature or laboratory analysis results to determine the quality of a medicine. Furthermore, only a few participants considered the manufacturer's reputation or visual examination of the pharmaceutical product as indicators of the quality of a medicine.

Nearly half of the participants in this phase of the study believed that the tender system used for medicine procurement in their settings focused on cheaper prices only. This was not surprising since reducing procurement costs is one of the key objectives of pharmaceutical tenders in any setting (WHO, 1999b). One quarter of the participants indicated that the current tender system did not consider the quality of the medicine manufacturers. It is possible that the participants may not be fully informed about the prequalification requirements of manufacturers to participate in the tender or they might believe that these prequalification requirements may not be adequate. Furthermore, a few participants highlighted that the current tender system caused frequent changes to the available medicines. This might be an area of concern particularly with chronic patients as it could lead to medicine non-adherence due to frequent changes to the medicines that they were comfortable using, as has also been reported as a concern by healthcare professionals in Germany and Denmark (Dylst, Vulto & Simoens, 2011).

The participants in this phase of the study had mixed views about the state of the current medicine storage and transporting conditions in MOI-MSD settings. The physicians' group, in particular, had more negative views about these conditions when compared with the pharmacists' group. Examples of concerns about medicine storage conditions included storage in areas exposed to heat, humidity and water leakage in rainy weather, pests found in the medicine storage area, medicine boxes not immediately placed on the warehouse shelves and not having a separate area for medicine storage away from other departments. The participants have also shared concerns about transportation conditions, where they reported that medicines were not arranged appropriately in transportation vehicles, exposure of medicine to heat and humidity during transportation, distant locations in the country to transport medicines from the main store in Riyadh and medicines transported by drivers with limited knowledge about appropriate medicine transportation conditions. In response to these concerns about medicine storage conditions, the participants recommended the establishment of new up to date standard medicine warehouses, embracing technology to facilitate medicine storage, monitoring storage conditions and establishing a new main store in each region of the country. Furthermore, the participants in this phase of the study recommended transporting medicines by other means including airplanes, including thermometers

with each medicine consignment, the training of staff responsible for medicine transportation, monitoring medicine transportation conditions and direct delivery of medicines from suppliers to the primary clinic warehouses. However, international guidelines (WHO, 2003b; DELIVER, 2003; WHO, 2007) for appropriate medicine storage and transportation conditions are available that could be followed in order to improve any possible defects in storage or transportation of medicines in these settings.

Nearly half of the participants in this phase of the study believed that expired medicines and nearly expired medicines are an issue of concern in MOI-MSD settings. The systematic review of literature (Chapter 3) had identified several studies that found expired medicines in their settings worldwide. These expired medicines could be a result of inappropriate quantification of required medicines during medicine procurement, suppliers delivering nearly expired medicines or poor distribution practices that could include dispensing a further expiry pharmaceutical product while a nearer expiry date product is available in stock. The participants had several recommendations to improve this situation, including the collection of accurate consumption data from all primary clinics, using computers to dispense medicine quantities according to the nearest available expiry product, monitoring expiry dates, suppliers to deliver only minimum acceptable expiry dates and to encourage medicine exchanges between MOI-MSD primary clinics and also other healthcare sectors in the country.

The majority of participants believed that the reporting of medicine quality problems was not activated in MOI-MSD settings, which would suggest a degree of under-reporting of such problems from different stakeholders at these settings. Some barriers to the reporting of medicine quality problem were identified in this study. A few participants indicated that the reporting mechanism was not clear to them: similar to other reports identified in the literature (Suyagh, Farah & Abu Farha, 2014; Toklu & Uysal, 2008; Bawazir, 2006; Khan, 2013). Other participants believed that the reporting method was paper-based and that there were no incentives to the reporter. It has been previously shown that electronic reporting systems and providing incentives to reporters

would contribute to an increase in the number of medicine-related problem reports such as adverse drug reactions (Pedrós et al., 2009; Linder et al., 2010; Cereza et al., 2010).

Furthermore, most participants in this phase of the study recommended establishing a department within the MOI-MSD to handle reports of medicine quality problems. A previous study has shown that establishing a network of physicians has increased the number of medicine-related problem reports such as adverse drug reactions and also introduced new reporters (Goldstein, Berlin, Saliba, Elias & Berkovitch, 2013). Other suggestions included increasing education about medicine quality problems and encouraging staff to report problems by offering incentives. It has been shown in previous studies that the rate of reporting of medicine-related problems such as adverse drug reactions could be improved through educational intervention and advocacy (Clarkson, Ingleby, Choonara, Bryan & Arlett, 2001; Mehta et al., 2007).

Several strategies to enhance quality assurance of medicines have been discussed in this phase of the study. Medicine monitoring divided opinion between participants, where some believed it was excellent, others believed it was improving, while some believed it was non-existent in these settings. The meaning of medicine monitoring also incited different opinions, where some believed it was comprehensive throughout the medicine cycle while others focused on medicine storage and/or dispensing to patients. The WHO has indicated that medicine monitoring can be achieved through all medicine stages, including manufacture, procurement, storage, transportation and, following use by the patient, for possible complaints (WHO, 2007).

Medicine analysis was another strategy to enhance quality assurance that was discussed in this study. Nearly half of the participants in this study believed that the SFDA was responsible for conducting medicine analysis, since it would be demanding in terms of resources for it to be conducted within MOI-MSD settings. Some specified the role of the MOI-MSD within this context to send samples to the SFDA and receive analysis reports. The participants recommended sending samples to the SFDA frequently, that the SFDA should establish at least one medicine laboratory in each region in the

country, and that suppliers should include batch analysis reports with each medicine consignment delivered to the MOI-MSD, as a means of improving medicine analysis.

Establishing a department or a committee to monitor medicine quality was another strategy for ensuring quality assurance, which was discussed with the participants in this phase of the study. Almost all participants supported the establishment of such a department or committee, in order to monitor medicine quality problems, research patients' satisfaction with medicines, educate staff about medicine quality problems and to act as a link between the MOI-MSD and SFDA to ensure rapid communication between the two organisations. Furthermore, the participants recommended that the department or committee should be centralised in Riyadh, have representatives in clinics, employ a sufficient number of staff, train their staff and use electronic means of communication in order to achieve the required objectives.

The participants in this phase of the study discussed several potential factors affecting medicine supply. The majority of participants believed that medicine country of manufacture, medicine availability and medicine price were important factors affecting supply decisions. Country of manufacture was perceived as an important factor since different countries have a different capacity of monitoring medicines, importing medicine from distant countries could result in medicine shortages and political relationships between the supplying country and the importing country could be a major factor in the supply decisions. It has been previously reported that medicines from developed countries such as China and India were treated with some suspicion by healthcare providers in South Africa (Patel et al., 2012).

Medicine availability was perceived as being preferred by healthcare professionals and patients since medicines are the core of the services provided by MOI-MSD primary clinics to patients: non-availability may raise suspicion and have other possible impacts on patients such as medicine non-adherence, health deterioration or patients using the wrong alternative medicine. Medicine price was viewed as an important factor in patients' acceptance of the medicines: higher medicine prices would guarantee better quality, and medicine price is a major component of governmental regulations in tender

procurement. The WHO considers both medicine price and availability as essential indicators of medicine accessibility (WHO, 2008).

In contrast, the participants in this phase of the study largely perceived other potential factors influencing medicine supply as not being important. The experience of a friend or a family member was believed to be unimportant since it is not based on reliable professional judgment and patient reactions and preferences for medicines differ considerably. Patient preference was also considered to be of minimal importance since it is not possible to please all patients. Perhaps these negative views about the importance of patient's experience with the supply of medicines were influenced by limited perceptions of medicines within a socio-cultural context (Patel et a., 2010; Patel et al., 2012). The medicine information leaflet was not considered important since the majority of patients do not read them; they contain scientifically bias information, have unnecessary information about extremely rare diseases and are difficult to read due to small font size. Previous studies have shown that medicine information leaflets on branded medicines differed from generic alternatives in Saudi Arabia (Gebran & Al Haidari, 2006; Al-aqeel, 2012). Such differences could hinder the confidence of healthcare professionals in their content and therefore may not be considered as an attribute that could affect medicine supply decisions.

Strengths and limitations of this phase of the study

This phase of the study used telephone interviews as a means for data collection with the participants. The use of telephone interviews could have several advantages for the purpose of this phase of the study such as practicality when the researcher and the participants are located in different countries, cheaper costs for conducting interviews and may increase the comfort of the participants when interviews are conducted while they are in their homes, for example. In contrast, telephone interviews could limit the interviewer's ability to observe the participant's body language and technical difficulties may be encountered during the interview process. Technical difficulties during tape recording of the interviews were only encountered once and were immediately and simply resolved by terminating the call and restarting the interview from the point that had already been reached. This study had a limited sample size and

did not seek data saturation since the objectives of this study were to clarify ambiguous responses and validate results from a previous survey phase of the study (Chapter 6 phase 4). Only one female healthcare provider offered to participate in this study, which could be explained by cultural barriers between males and females in the country.

Nevertheless, this phase of the study had several strengths, including being one of the few studies that explored issues around medicine quality and related issues from a social and qualitative approach worldwide and in Saudi Arabia. This phase of the study had also validated and explained some of the findings in a previous phase of the study.

The following chapter triangulated the evidence collected from the different phases of this study and discussed the overall findings of the MOI-MSD stakeholders' perceptions about medicine quality and any related issues.

7 Chapter 7: Overall results and discussion of stakeholders' perceptions about medicine quality and related issues

This chapter combines all results obtained from the previous chapter (Chapter 6) regarding the stakeholders' perceptions about medicine quality and its related issues, which was followed by an overall discussion of the findings and a final conclusion to this chapter. The shared themes were identified among all MOI-MSD stakeholders through triangulation of the available data in addition to some individual themes and sub-themes to the patients, physicians and pharmacists in this study.

7.1 Overall results of stakeholders' perceptions

The results obtained from the different phases of this study have identified five shared themes among the different stakeholders in MOI-MSD settings. These shared themes included beliefs about medicine quality, knowledge about medicine quality, experiences of and behaviour towards medicines with doubtful quality, challenges to medicine quality in the MOI-MSD and recommendations to improve medicine quality within these settings.

Additionally, patients' and healthcare providers' individual themes and sub-themes were identified from the findings of the different phases of the study. Patient's individual themes and sub-themes included their knowledge and beliefs about medicines and their quality, the relationship between medicine price and disease severity, counterfeit medicines, challenges they encountered in MOI-MSD clinics and their trust in the healthcare providers. The pharmacists' and physicians' individual themes and sub-themes included the pharmacist's role in MOI-MSD, beliefs and views about medicine quality, the tender system for medicine procurement, medicine therapeutic classes and formulations of quality concern, reporting medicine quality issues, storage and transportation of medicines within the MOI-MSD, patients' acceptance of their medicines and recommendations to enhance quality assurance.

7.1.1 Shared theme 1: Beliefs and views about medicines and their quality

Most commissioners (5/6) and physicians (71%) in this study believed that the quality of medicines in Saudi Arabia was good or excellent. To a lower extent, more than half of the pharmacists (55%) and patients (58%) agreed with these views. However, the number of stakeholders that believed that the quality of medicines in MOI-MSD settings were good or excellent was found to be constantly lower, than what is available in the Saudi Arabian market in the opinion of commissioners (17%), physicians (52%) and pharmacists (36%) but not the patients (71%).

More than half of the commissioners (4/6), physicians (83%), pharmacists (83%) and patients (62%) in this study believed that more than 10% of the global pharmaceutical supply chain was counterfeit. Similarly, the estimations about the prevalence rate of counterfeit medicines in Saudi Arabia were more than 10% of the local pharmaceutical supply chain in the opinion of commissioners (4/6), physicians (68%), pharmacists (57%) and patients (57%).

All stakeholders in this study shared some common beliefs about medicines and their quality. Such beliefs included the conception that developed countries manufactured better quality medicines when compared with developing countries. Furthermore, the physicians, pharmacists and patients believed that the quality of medicines was different according to the manufacturer and the hospital that dispensed the medicine in Saudi Arabia. Moreover, all stakeholders reported that patients frequently demanded medicines by their brand name although medicines worked differently for various individuals.

The stakeholders in this study identified several sources of information regarding the quality of their medicines. Their personal experience with regard to using a medicine, or the experience of a patient or healthcare staff, was considered a reliable source of information about medicine quality in the opinion of all stakeholder groups. The commissioners in this study have also identified circular letters they received from the SFDA as a source of information for medicine quality. Research studies and laboratory testing were only identified as being important by physicians and pharmacists in this

study. Further details regarding this theme can be found in Tables 7.1 and 7.2 in addition to Appendix 25.

Table 7.1 Stakeholders' opinions on quality of medicines

Sub-theme	Characteristics	Commissioners	Physicians	Pharmacists	Patients
Medicine quality in Saudi Arabia	Good/excellent	5/6	45/63 (71%)	32/58 (55%)	31/53 (58%)
	Average	1/6	14/63 (22%)	23/58 (38%)	15/53 (28%)
	Poor/unacceptable	-	4/63 (6%)	3/58 (5%)	5/53 (9%)
	No answer	-	-	-	2/53 (4%)
Medicine quality in MOI-MSD	Good/excellent	1/6	33/63 (52%)	21/58 (36%)	38/53 (71%)
	Average	4/6	22/63 (35%)	19/58 (33%)	6/53 (11%)
	Poor/unacceptable	1/6	8/63 (13%)	18/58 (31%)	5/53 (9%)
	No answer	-	-	-	4/53 (8%)
Percentage of counterfeit medicines globally	0% to 10%	2/6	7/63 (11%)	5/58 (9%)	12/53 (23%)
	20% to 50%	2/6	39/63 (62%)	32/58 (55%)	18/53 (34%)
	60% or more	2/6	13/63 (21%)	16/58 (28%)	15/53 (28%)
	No answer	-	4/63 (6%)	5/58 (9%)	8/53 (15%)
Percentage of counterfeit medicines in Saudi Arabia	0% to 10%	2/6	16/63 (25%)	20/58 (34%)	17/53 (32%)
	20% to 50%	2/6	27/63 (43%)	19/58 (33%)	19/53 (36%)
	60% or more	2/6	16/63 (25%)	14/58 (24%)	11/53 (21%)
	No answer	-	4/63 (6%)	5/58 (9%)	6/53 (11%)

Table 7.2 Stakeholders' beliefs and source of information about medicine quality

Sub-theme	Characteristics	Commissioners	Physicians	Pharmacists	Patients
Beliefs about medicines and their quality	Developed countries manufacture superior quality medicines				
	Medicine quality differs between manufacturers in Saudi Arabia				
	Medicine quality is different between hospitals in Saudi Arabia	-			
	Patients frequently demand brand medicines				
	Medicines do not work similarly for all people				
Source of information about medicine quality	Patient's experience				
	Personal experience				
	Staff experience				
	Family/friend experience		-	-	
	SFDA letters		-	-	-
	Research studies	-			-
	Laboratory tests	-			-
	Manufacturer reputation	-		-	-
	Visual check of medicine	-	-		-
	Storage condition	-	-		-

7.1.2 Shared theme 2: Knowledge about medicine quality and their problems

Members from all stakeholder groups identified a good quality medicine as a medicine with good effect and from a brand manufacturer. The reasonable medicine price was a characteristic of a good quality medicine in the opinion of commissioners, physicians and pharmacists but not the patients in this study. Furthermore, the physicians and pharmacists in this study highlighted medicine availability, safety and long expiry dates as important characteristics of a good quality medicine.

A counterfeit medicine was believed to be a medicine with an effect problem by participants and respondents from all stakeholder groups in this study. Commissioners and pharmacists considered problems with the appearance of a medicine as a characteristic of a counterfeit medicine. Moreover, participants from the physician' and patient' groups believed that expired and generic medicines were counterfeit. Further details about this theme can be found in Table 7.3 and Appendix 26.

Table 7.3 Stakeholders' knowledge about medicine quality

Sub-theme	Characteristics	Commissioners	Physicians	Pharmacists	Patients
Characteristics of a good quality medicine	Has good effect				
	From a brand company				
	Has good appearance		-		-
	Has reasonable price				-
	Is registered		-		-
	Has good manufacturing	-			
	Is accepted by patients			-	
	Is available	-			-
	Is safe	-			-
	Has good expiry dates	-			-
Characteristics of a counterfeit medicine	Effect problem				
	Manufacturing problem	-			
	Appearance problem		-		-
	Content API problem				-
	Fake copy of original	-			
	From unreliable source	-			
	Not registered in SFDA	-			
	Is a generic medicine	-		-	
	Is an expired medicine	-		-	
	Has storage problem	-		-	

7.1.3 Shared theme 3: Experiences with and behaviour towards doubtful quality medicines

Less than one-third of physicians (21%), pharmacists (36%) and patients (38%) reported having any previous experience with a doubtful quality medicine. However, this was not the case with commissioners, where two-thirds of them (4/6) have reported past experiences with such doubtful quality medicines.

All stakeholders particularly from the commissioner group (4/6) described their experience with a doubtful quality medicine in terms of a medicine that did not have the desired effect. However, there were various other experiences with medicine quality concerns that were commonly described by the commissioners and pharmacists, in particular, a problem with medicine appearance, undesired odour or the presence of less than stated dosage numbers. A detailed account of the reported quality concerns and stakeholders' experiences can be found in Table 7.4.

The majority of physicians (56%) and some pharmacists (40%) indicated that they have not received reports about doubtful quality medicines on an annual basis. In contrast, one-half of the commissioners (3/6) indicated they routinely received one report every year regarding medicine quality concerns while the other half (3/6) highlighted that they received ten or more of these reports each year.

All stakeholders in this study including the commissioners (3/6), physicians (22%), pharmacists (52%) and patients (8%) shared the same behaviour, reporting medicine quality concerns, but with various degrees, to the higher MOI-MSD administration and/or the SFDA. In particular, patients responded that they would probably stop using the medicine (70%) and/or inform their physician (42%) when they have such doubts about the quality of medicines. Further details can also be found in Table 7.4.

Table 7.4 Stakeholders' experiences and behaviour about medicines with doubtful quality

Sub-theme	Characteristics	Commissioners	Physicians	Pharmacists	Patients
Previous experience with doubtful quality medicines	Yes	4/6	13/63 (21%)	21/58 (36%)	20/53 (38%)
	No	2/6	48/63 (76%)	37/58 (64%)	23/53 (43%)
	No answer	-	2/63 (3%)	-	10/53 (19%)
Type of experience with doubtful quality medicines	Medicine non-effective	4/6	4/63 (6%)	2/58 (3%)	13/53 (25%)
	Medicine side effects	-	-	-	7/53 (13%)
	SFDA failure letters	2/6	-	2/58 (3%)	-
	Expired medicines	-	1/63 (2%)	-	-
	Missing expiry date	-	-	1/58 (2%)	-
	Medicine not registered	-	-	2/58 (3%)	-
	Appearance problem	1/6	-	5/58 (9%)	-
	Medicine had bad odour	1/6	-	1/58 (2%)	-
	Less than stated doses	-	-	1/58 (2%)	-
	Tablets did not dissolve	3/6	-	-	-
Number of annual reports about doubtful quality medicines	None	-	35/63 (56%)	23/58 (40%)	Not applicable
	Once a year	3/6	14/63 (22%)	12/58 (21%)	
	2 to 4 times a year	-	6/63 (10%)	12/58 (21%)	
	5 to 10 times a year	-	1/63 (2%)	7/58 (12%)	
	More than 10 times	3/6	5/63 (8%)	4/58 (7%)	
Behaviour when in doubt about medicine quality	Report to authority	3/6	14/63 (22%)	30/58 (52%)	4/53 (8%)
	Report to pharmacist	-	25/63 (40%)	12/58 (21%)	3/53 (6%)
	Report to the Director of pharmacy	-	31/63 (49%)	35/58 (60%)	-
	Report to physician	-	11/63 (17%)	16/58 (28%)	22/53 (42%)
	Find alternative medicines	2/6	1/63 (2%)	2/58 (3%)	12/53 (23%)
	Stop medicine use	-	35/63 (56%)	15/58 (26%)	37/53 (70%)
	Do not take action	-	4/63 (6%)	2/58 (3%)	6/53 (11%)

7.1.4 Shared theme 4: Challenges to medicine quality in MOI-MSD

All stakeholder groups in this study identified medicine procurement based solely on price differences, the difficulty in reporting medicine quality problems and medicine storage conditions as common challenges to medicine quality in MOI-MSD settings. Moreover, commissioners and healthcare providers (i.e. pharmacists and physicians) added the outdated medicine formulary and the limited budget available to procure medicines as additional challenges. Furthermore, patients and commissioners highlighted medicine non-availability as a challenge to medicine quality in these settings. Further details can be found in Table 7.5 and Appendix 27.

Table 7.5 Stakeholders' perceptions about challenges to medicine quality in MOI-MSD

Sub-theme	Commissioners	Physicians	Pharmacists	Patients
Tender procurement of medicines is based on price not quality				
Limited or difficulty in reporting medicine quality problems				
Medicine storage conditions				
Medicine transport conditions	-			-
Expired medicines	-			-
Nearly-expired medicines	-			-
Limited budget available to procure medicines				-
Outdated medicine formulary				-
Inadequate medicine monitoring	-			
Patients do not accept their medicines	-			-
Medicine non-availability		-	-	

7.1.5 Shared theme 5: Recommendations to improve medicine quality in MOI-MSD

Participants and respondents from all stakeholder groups have recommended improving medicine monitoring, medicine analysis, procurement of medicines, and conducting educational campaigns about medicines and their quality as a means to improve medicine quality in MOI-MSD settings. The physicians, pharmacists and patients have also suggested improvements to medicine storage conditions and communication between staff and patients. Furthermore, the healthcare providers in this study have suggested establishing a medicine quality department or committee within the MOI-MSD in order to focus on medicine quality issues. A comprehensive list of all stakeholders' recommendations can be found in Table 7.6 and Appendix 28.

Table 7.6 Stakeholders' recommendations to improve medicine quality in MOI-MSD

Sub-theme	Commissioners	Physicians	Pharmacists	Patients
Improve medicine monitoring				
Improve medicine analysis				
Improve medicine procurement system				
Educational campaigns about medicine quality				
Improve medicine storage conditions	-			
Improve medicine transport conditions	-			-
Ensure medicine expiry dates	-			
Improve communication among staff and with patients	-			
Update the local medicine formulary		-		-
Conduct further research on medicines		-		-
Establish a department or a committee for medicine quality	-			-

7.1.6 Individual stakeholders' themes and sub-themes

This study identified some themes and sub-themes, which were unique to the patients' group of participants. It was found that more than one quarter of patients overall (26%) did not know the name of their medicines, particularly those from the chronic sub-group of patients (31%). Some patients have also expressed some beliefs about medicines that were not shared with other stakeholders in this study, such as the belief that increased severity of a disease would increase the related medicine price (8%) and that increased medicine strength would increase its quality (6%). Moreover, counterfeit medicines were believed to be increasing recently in Saudi Arabia (8%) and counterfeiting was mostly associated with herbal medicines or cosmetic products in the country rather than pharmaceutical products (8%). The patients have also expressed concerns about several difficulties they encountered that are associated with MOI-MSD clinics, such as inconvenient locations and opening times (23%). Furthermore, patients have expressed their trust in their physicians (55%) more often than their pharmacists (8%). More details regarding patients' specific themes and sub-themes are available in Table 7.7.

Similarly, the follow-up interviews with pharmacists and physicians generated some unique themes and sub-themes, in addition to further details about previously identified themes and sub-themes from the survey questionnaire phase of the study. The role of the pharmacist in MOI-MSD settings was largely foreseen as educational regarding the medicine by both physicians (5/8) and pharmacists (6/8). Physicians (3/8) and pharmacists (4/8) have indicated that patients in MOI-MSD settings accepted the available medicines on most occasions. Moreover, the physicians and the pharmacists have provided further details to some of their recommendations to enhance the quality assurance of medicines in MOI-MSD settings. Such recommendations included improvement to medicine monitoring, medicine analysis, medicine supply practices, reporting of medicine quality problems and the establishment of a medicine quality department or committee within the MOI-MSD. Further details regarding the healthcare providers' individual themes and sub-themes can be found in Table 7.7.

Table 7.7 Individual stakeholders' themes and sub-themes

Themes	Sub-themes	Patients	Physicians	Pharmacists
Knowledge about medicines	Do not know the name of their medicines	14/53 (26%)	-	-
Beliefs about medicines	Higher strength medicines have more quality	3/53 (6%)	-	-
	Severe diseases medicines are more expensive	4/53 (8%)	-	-
Counterfeit medicines	Increasing lately in Saudi Arabia	4/53 (8%)	-	-
	Only exist in herbal medicines and cosmetics	4/53 (8%)	-	-
Challenges to patients in MOI-MSD clinics	Clinics inconvenient locations and times	12/53 (23%)	-	-
	Hospital appointments take too long	3/53 (6%)	-	-
	Excessive quantity of dispensed medicines	2/53 (4%)	-	-
Patient's trust	Patients completely trust their physicians	29/53 (55%)	-	-
	Patients completely trust their pharmacists	4/53 (8%)	-	-
Perceptions about pharmacist's role in MOI-MSD	Educational role about medicines	-	5/8 (63%)	6/8 (75%)
	Dispense medicines appropriately	-	4/8 (50%)	3/8 (38%)
	Protect from medication errors	-	2/8 (25%)	2/8 (25%)
	Comprehensive role in medicine cycle	-	1/8 (13%)	3/8 (38%)
	Can be improved by education	-	5/8 (63%)	3/8 (38%)
	Can be improved by counselling patients	-	-	3/8 (38%)
	Can be improved by becoming more active	-	2/8 (25%)	1/8 (13%)
Patients' acceptance of available medicines in the MOI-MSD	Patients mostly accept their medicines	-	3/8 (38%)	4/8 (50%)
	Patients do not accept the available medicine	-	1/8 (13%)	2/8 (25%)
	Can be improved by selecting better medicines	-	4/8 (50%)	3/8 (38%)
	Can be improved by staff re-assurance about quality of available medicines	-	2/8 (25%)	1/8 (13%)
Recommendations to enhance quality assurance in the MOI-MSD	Establish a department to monitor medicine quality	-	4/8 (50%)	3/8 (38%)
	Improve communication with SFDA	-	1/8 (13%)	1/8 (13%)
	Suppliers to include batch analysis certificates	-	-	1/8 (13%)
	Provide incentives to staff to encourage reporting	-	1/8 (13%)	2/8 (25%)
	Establish an electronic reporting system	-	1/8 (13%)	1/8 (13%)
	Involve other departments in medicine procurement	-	4/8 (50%)	2/8 (25%)
	Procure the same medicines for chronic patients	-	1/8 (13%)	1/8 (13%)
	Add quality criterion in the selection process	-	-	1/8 (13%)
	Learn from other hospital procurement experiences	-	1/8 (13%)	-
	Establish warehouses up to international standards	-	3/8 (38%)	2/8 (25%)
	Collect statistical data of dispensed medicines	-	1/8 (13%)	4/8 (50%)
	Transport medicines via airplanes	-	2/8 (25%)	1/8 (13%)
	Transport medicines by a distributing company	-	-	3/8 (38%)
	Include a thermometer in medicine consignments	-	2/8 (25%)	-

7.2 Overall discussion of stakeholders' perception

Stakeholders in this study commonly defined a good quality medicine in terms of achieving a desired therapeutic effect. Similar findings were identified in the literature among patients and healthcare providers in developing countries (Syhakhang et al., 2004; Patel et al., 2010; Patel et al., 2012). Interestingly, only a limited number of stakeholders in this study have indicated that the registration status of a medicine would be a guarantee of a good quality medicine. This result is in contrast to the healthcare commissioners' views in Sudan (Alfadl et al., 2013) and medicine wholesalers' views in Cambodia (Khan et al., 2011), as reported in a previous studies. A possible explanation of this finding is that various stakeholders in this study could have limited trust in or knowledge about medicine registration processes; which would indicate a need for the regulatory agency in the country, the (SFDA), to increase awareness and share information about medicine registration and/or surveillance with various stakeholders.

The most common definition of counterfeit medicines among all stakeholders in this study is that they have an effect problem, whether there was no effect or limited therapeutic effect. This finding did not mirror the results from previous studies with commissioners in Sudan (Alfadl et al., 2013) and managing executives in Cambodia (Khan et al., 2011). Only a limited number of stakeholders provided technical specifications regarding chemical analysis results, packaging appearance and medicine source to describe a counterfeit medicine despite the WHO emphasis on these elements (WHO, 1999a). This would suggest the need to raise stakeholders' awareness, particularly from within the physicians' and patients' groups, about the nature of counterfeit medicines in order to minimise confusion with other medicine related issues such as expired or generic medicines that have been previously reported among patients in the literature (Sarradon-Eck et al., 2007; Håkonsen & Toverud, 2011).

Most stakeholders believed that the quality of medicines in Saudi Arabia was good or excellent. However, there were some differences noted in their views about the quality of medicines within the MOI-MSD settings. Around one third of pharmacists rated the quality of medicines in the MOI-MSD as poor or unacceptable, more than physicians or commissioners. These views could be explained by the way that pharmacists consider

themselves as guardians of medicines (Alhamarnah, Rosenthal, McElnay & Tsuyuki, 2011) and, therefore, could be over-protective about the quality of medicines in their own settings. Nevertheless, it should be noted that the differences between the pharmacists' and physicians' perceptions about medicine quality in both the MOI-MSD and in Saudi Arabia was found to be statistically insignificant as shown in Table 6.12. In contrast, almost three-quarters of patients believed that the quality of medicines in MOI-MSD settings was good or excellent. This surprising finding could be explained by the relative success of healthcare commissioners and providers in the protection of patients from receiving medicines with questionable quality. It is also possible that patients could be grateful for receiving medicines free of charge in the MOI-MSD settings and, therefore, do not attempt to question their quality.

Around two-thirds of participants from all stakeholders groups in this study believed that the counterfeit medicines prevalence rate was more than 10% of the pharmaceutical supply chain both globally and in Saudi Arabia. These reported findings are more in line with media predictions of 30%-40% in Saudi Arabia (Saudi Gazette, 2011) than the figure the WHO estimates currently to be 10% (Cockburn et al., 2005; Heyman et al., 2011; Ziance, 2008) or what the SFDA predicts at 0.5% (Arabnews, 2010). However, the most likely explanation of these estimates are lack of knowledge within all stakeholder' groups about counterfeit medicines rather than genuine concerns about their high incidence in the country as previously discussed.

The sources of information regarding medicine quality varied considerably among the different stakeholders in this study. The healthcare commissioners and providers mostly used experience from the actual use of a medicine as a source of information about its quality. However, about half of the patients indicated that the physician's recommendation was the only necessary source of information they needed regarding medicine quality. This result indicates the patients' trust in their physicians and would suggest that any future educational programmes would probably be best delivered directly from the physician to the patient.

Past experiences with questionable quality medicines varied between different stakeholders. The majority of commissioners believed that they had encountered questionable quality medicines within MOI-MSD settings in the past. However, the majority of healthcare providers (i.e. pharmacists and physicians) did not believe that they had past experiences with questionable quality medicines. Patients' opinions were split in half, where one half believed that they have previously encountered medicines with questionable quality, while the other half did not. The majority of these reported experiences cannot be confidently attributed to genuine experiences with questionable quality since they have been described as experiences with medicine effects. However, a number of experiences reported by pharmacists from both the commissioner' and healthcare provider' groups could be attributed to medicine quality problems, such as experiences with medicines that did not have an expiry date, a medicine with an appearance problem, a medicine with bad odour, a medicine that contained less than the stated dosage form and tablets that did not dissolve. The majority of these experiences have been reported in previous studies as shown in Chapter 3 of this thesis.

The stakeholders in this study reported a range of behaviours, when in doubt about the quality of medicines. Reporting the concern about medicine quality to the higher authorities, including the SFDA, was reported by half of the pharmacists in the commissioner' and healthcare provider' groups but was less reported in the physicians' and patients' groups. This would indicate more knowledge among pharmacists about the significance of reporting medicine quality concerns on a national level. Furthermore, reporting these concerns internally to the Director of Pharmacy in the healthcare providers' group and to the physician in the patient group was also documented. More than half of the physicians and patients in this study considered stopping prescribing or using the medicine, if they had doubts about a medicine's quality, while only one quarter of the pharmacists in the healthcare provider' group and none from the commissioner' group considered stopping dispensing these medicines. It is possible that pharmacists did not feel they had the authority to stop dispensing medicines without clear instructions from their managers and/or physicians. Therefore, it is important to unify and communicate a clear plan of action to all stakeholders, when in doubt about the quality of medicines in these settings in order to clearly identify such concerns.

Reporting of medicine quality problems was a shared concern among all stakeholders in this study. It appears that some healthcare providers have limited knowledge of how to report, find paper-based documentation impractical and find that reporting such problems may not be rewarding for staff. These perceived barriers are not without support from the literature. Limited healthcare provider' comprehension about the correct method of reporting medicine-related problems was found with community pharmacists in Saudi Arabia (Bawazir, 2006; Khan, 2013), community pharmacists in Turkey (Toklu & Uysal, 2008) and pharmacists in Jordan (Suyagh et al., 2015), for example. Another less prevalent, yet evident, barrier to reporting medicine-related problems in this study was the lack of incentives for the reporter. This finding is in agreement with other results from a systematic review of the literature about barriers to adverse drug reaction reports (Lopez-Gonzalez, Herdeiro & Figueiras, 2009). In Saudi Arabia, the SFDA has both options for the public to report medicine quality problems, medication errors or adverse drug reactions on one single form that can be completed on either an electronic reporting system or a paper-based system (SFDA, 2015b). Thus, it is imperative to educate the stakeholders about such reporting options. Multiple research studies have demonstrated that implementing educational tools had a positive impact on increasing the rate of medicine related problem reports to support this recommendation (Clarkson et al., 2001; Mehta et al., 2007; Figueiras, Herdeiro, Polónia & Gestal- Otero, 2006; Herdeiro et al., 2012).

The stakeholders in this study believed that the medicine procurement system needed improvement and held the opinion that current tenders focused only on the price and not the quality of a manufacturer as determining supplier selection. It has been reported that different countries within the European Union use additional criterions in the selection of a supplier besides the best or cheapest offer, such as quality in Germany and impact on total healthcare budget in Slovenia (Dylst et al., 2011). Some pharmacists and physicians in this study have suggested the involvement of staff from other departments besides the Medical Supply Department in MOI-MSD settings. This recommendation is in line with the WHO recommendations for good procurement practices (GPP) that highlight the importance of dividing different steps of the procurement cycle between

different personnel or departments to minimise conflict of interest (WHO, 1999b). Another recommendation in this study was to provide specific consideration to chronic patients in the tender process, as it would result in frequent changes in the medicines supplied. This is in line with reported concerns about chronic patient adherence to their medicines in Germany, resulting from frequent changes in the medicines supplied through tender-based systems (Dylst et al., 2011).

The healthcare providers, i.e. the pharmacists and physicians at the primary care clinics, reported concerns about medicine storage and transportation within MOI-MSD settings on more occasions than commissioners or patients. This finding was surprising since the commissioners are the individuals who initiate medicine storage and transportation in these setting for the healthcare providers in the primary clinics. The results could indicate a gap in communication between the healthcare providers and the commissioners in the medicine supply cycle. This issue is important since extreme hot weather conditions could play a major role in the degradation of some medicines and therefore they could become substandard (Crichton, 2004; Naidoo et al., 2006). Furthermore, it has been reported in the literature that community pharmacists in Riyadh in Saudi Arabia expressed similar concerns about medicine storage and transportation conditions in their settings (Khoja et al., 2013a). The same study contained an observational part that found that around 10% of community pharmacies visited in Riyadh had temperature readings of >25°C (Khoja et al., 2013a). Therefore, it is recommended that commissioners in the MOI-MSD become aware of these issues and that storage and transportations conditions would be explored and examined in comparison to international (WHO, 2003b; DELIVER, 2003; WHO, 2007) and national guidelines (SFDA, 2012).

Several strategies have been proposed by the stakeholders in this study in order to enhance medicine quality assurance in these settings. All stakeholder groups' in this study considered medicine monitoring as a key strategy but with minimal description of what it entails. However, international guidelines provided by the WHO illustrate points beyond those which the stakeholders in this study have reported and indicate that monitoring medicines is an ongoing activity which starts at the time of medicine

manufacture, through procurement, storage, distribution, dispensing and monitoring complaints following use by the patient (WHO, 2007). The analysis of medicine samples is another strategy that has been reported by various stakeholders in this study in order to enhance quality assurance. There was a common belief held by healthcare providers, particularly from within the pharmacists' group, that the performance of laboratory medicine analysis was the responsibility of the SFDA and that the MOI-MSD responsibility was mainly to report and send medicine samples of questionable quality and then receive feed-back from the SFDA. This could be true since the WHO has indicated that one of the functions of a national regulatory agency in any country is the analysis of medicines during prequalification and registration stages (WHO, 2007). Moreover, the stakeholders have identified other strategies such as improvements to medicine procurement, storage, transportation and reporting of medicine quality problems that have been previously discussed. However, these strategies do not mirror the reported practices in South Africa (Patel et al., 2009) or Cambodia (Khan et al., 2011).

A number of medicine attributes that could affect medicine supply decisions have been identified in this study. The country of manufacturing was considered significant particularly from the pharmacists' and physicians' views. Previous research has suggested the medicine wholesalers in Cambodia considered the reputation of the manufacturer during their medicine procurement practices (Khan et al., 2011). The availability of medicines was considered an important factor in the supply of medicines according to the opinions of healthcare providers in this study. However, none of the healthcare providers and only one commissioner had identified medicine availability as a challenge in the MOI-MSD settings. In contrast, a significant number of patients, particularly those from Jeddah city, had complained of medicine non-availability. This would suggest a lack of knowledge or awareness about the patient-related issues with medicine use in these settings on both the commissioner and healthcare providers' part. It is important to note that the WHO considered medicine accessibility, which largely depends on medicine price and availability, as a basic human right that needs to be preserved at all costs (WHO, 2008). Furthermore, medicine non-availability is a global problem that could be identified in many developing countries (Cameron, Ewen, Ross-

Degnan, Ball, & Laing, 2008). Therefore, it is recommended that these findings be communicated to the healthcare commissioners and providers within the MOI-MSD to raise awareness about medicine non-availability in these settings. Furthermore, medicine prices were another factor that had been associated with supply decisions according to the physicians and pharmacists in this study. The Saudi Arabian governmental regulations regarding procurement in tenders support these perceptions with specific consideration of the selection of the least price of otherwise similar products (MOF, 2006).

Overall strengths and limitations of the stakeholders' perception study

This study was among the few studies that explored the perceptions of stakeholders about medicine quality and related problems worldwide and the first in Saudi Arabia to the researcher's knowledge. It had systematically explored the issue from the perspective of commissioners who make medicine supply decisions, physicians who prescribe the medicines, pharmacists who dispense medicine and patients who ultimately use the medicine within the MOI-MSD settings in Saudi Arabia. The common and specific themes and sub-themes were identified among the different stakeholder groups in this study.

However, this study is not without its limitations. In the interview phases of the study, generalisability of results and data saturation was not achieved, as the purpose of the study was exploratory. Some questions were concerned with the participants' previous experiences and therefore could be a subject of recall bias. Female participants were limited in the study particularly in the commissioners and healthcare provider groups due to cultural difficulties that would limit their presence in the MOI-MSD administration and the researcher's access to them in primary care clinics. It was not possible to send the interview transcripts back to patients via e-mail as they have only provided their telephone numbers for future contact. The results were frequently displayed in numbers and percentages; however, caution is advised when interpreting such data from the small number of participants available in the commissioners' group or interviews with pharmacists and physicians. Moreover, the questionnaire survey part of the study also had some limitations. The identity of respondents cannot be verified

since the questionnaire survey was anonymous. No further clarification of questions by the researcher was possible as the questionnaire was self-completed. Furthermore, there were other members of the healthcare staff at the MOI-MSD who did not participate in this study, such as nurses, technicians or other administrative staff in these settings.

7.3 Conclusion

The majority of all stakeholders in this study (i.e. commissioners, physicians, pharmacists and patients) perceived the quality of medicines in Saudi Arabia as good or excellent. However, healthcare commissioners and providers (i.e. physicians and pharmacists) mostly perceived that the quality of medicines in the MOI-MSD was of a lower quality than that available elsewhere in Saudi Arabia, while patients mostly did not share these views. Thus, quality assurance strategies should target healthcare commissioners and providers in these settings.

Most stakeholders estimated that counterfeit medicines are more prevalent than has been estimated by the local authorities (SFDA) or international organisations (WHO). This could be attributed to their understanding of what a good quality or a counterfeit medicine was, which was found to be mostly associated with medicine effect, with minimal regard to the medicine source or the technical attributes of the medicine such as packaging, source, chemical or physical analysis results. Therefore, an educational campaign is needed to increase the awareness of all stakeholders about the nature of counterfeit medicine and local or international prevalence estimations, to minimise unnecessary fear, which could impact medicine accessibility.

Furthermore, there were common beliefs mostly shared among healthcare commissioners and providers, such as that a higher medicine price indicated a higher quality medicine; that developed countries manufactured better quality medicines than developing countries and that patients preferred to use brand medicines. However, the majority of patients did not agree with these views, particularly female and chronic patients. It is, therefore, suggested that encouragement is given to improve communication between healthcare commissioners/providers and patients, to assess their requirements and concerns. An example of such patient requirements or concerns was found in relation to medicine non-availability particularly in Jeddah city, which was not identified as a challenge by most healthcare commissioners or providers. Instead, healthcare providers and some commissioners highlighted other medicine challenges such as nearly expired medicines, procurement tenders that focus on price rather than quality and inadequate medicine storage and/or transportation conditions. Furthermore,

all stakeholders agreed that the reporting of medicine quality problems within the MOI-MSD was not clear and/or difficult. This would suggest that educating all stakeholders about procedures to report such problems and increasing the options for reporting medicine quality concerns such as electronic or telephone methods of reporting requires improvement.

Moreover, nearly half of participants from all stakeholders groups believed that they had previous experiences with questionable quality medicines. However, details of such experiences rarely reflected reliable medicine quality concerns, with the exception of pharmacists in this study. Most of the reported medicine quality experiences involved the use of a medicine that had no or limited effect, which could be associated with a wide variety of issues, in addition to medicine quality problem. Therefore, it becomes imperative to educate the stakeholders, particularly physicians and patients, about medicine quality problems and how to detect them.

All stakeholders in this study agreed that it was necessary to improve medicine monitoring, analysis, procurement and communication regarding the reporting of such problems, in order to improve the quality of medicines within the MOI-MSD settings as they were perceived as major challenges to medicine quality.

8 Chapter 8: Overall discussion of the research

Medicines provided to patients should be ensured in terms of safety, efficacy and quality in all healthcare settings. Medicine quality problems, whether medicines are counterfeit or substandard, are increasing worldwide (Cockburn et al., 2005; Caudron et al., 2008; PSI, 2014a). This alarming increase in the prevalence rates should be considered together with the possibility of negligence, to consider medicine quality problems in cases of treatment failure, which is often associated with the disease progression rather than the medicine itself (deKieffer, 2006; Liang, 2006; Newton et al., 2008; Feldschreiber, 2009; Davison, 2011). Nevertheless, evidence has been shown to associate medicine quality problems with mortality in severe cases (Cockburn et al., 2005; Mackey & Liang, 2011; Kao et al, 2009). Furthermore, medicine quality problems could also have a negative impact on the patient in terms of morbidity, drug resistance, therapeutic failure or possible toxicity (Cockburn et al., 2005; Amin & Kokwaro, 2007; Jackson, 2009). Other dimensions of the negative impact of counterfeit and substandard medicines could be in the economic burden they may cause on the individuals involved and on societies as a wholes (Yankus & Marks, 2009; Wertheimer & Norris, 2009), as well as the impact on loss of trust in healthcare providers and healthcare settings (Cockburn et al., 2005; Amin & Kokwaro, 2007; Wertheimer & Norris, 2009; Mackey & Liang, 2011; Kyriacos et al., 2008). Therefore, the issue of substandard and counterfeit medicines was considered significant and needed to be addressed in this study.

The quality of medicines has been traditionally determined in laboratory settings, by conducting chemical and physical testing of medicine samples, to test their conformity to various pharmacopoeial specifications (Patel et al., 2010). It is also important to authenticate the source and packaging information of a medicine sample in order to exclude the possibility of counterfeit medicines (WHO, 1999a; IMPACT, 2011). Another paradigm, possibly less explored, of medicine quality and related problems is through the social paradigm, by investigating the stakeholders' perceptions. Therefore, chemical laboratory testing, authentication of source and packaging information, in addition to investigating the stakeholders' perceptions including healthcare

commissioners, providers and patients was the approach of choice in this study. To the researcher's knowledge, this was the first study with a pragmatic approach to consider the issue of medicine quality and related problems in terms of chemical laboratory testing, visual inspection of medicine source and packaging, in combination with the stakeholders' perceptions about medicine quality and any related problems.

The first part of this study was concerned with conducting a systematic detail about the nature of evidence pertaining to counterfeit and substandard medicines in the published literature from a traditional laboratory based perspective. This study found that the majority of studies were conducted in certain parts of Asia and Africa, while only two studies were conducted in the Middle East (Kyriacos et al., 2008; Abdo-Rabbo et al., 2005). The majority of studies were found to have investigated medicines for the treatment of infectious diseases, while extremely limited studies were reported on chronic disease medicines. Less than 10% of all identified studies have attempted to authenticate the source of the medicine and to inspect the medicine package information to account for the possibility of counterfeiting to supplement chemical analysis tests. The nature of problems found in this systematic review was found to relate more to substandard medicines rather than counterfeiting, which would agree with previous publications (Caudron et al., 2008). More specifically, the majority of problems identified in this study reported inadequate amounts of API concentrations and only a few studies reported the wrong API or absence of any API in the medicine samples. Furthermore, it was found that HPLC was the instrument of choice to conduct chemical analysis tests in most of the identified studies. Recent findings from the research studies since the publication of this systematic review were similar to the cited literature in the review (Khurelbat et al., 2014; Chikowe, Osei-Safo, Harrison, Konadu & Addae-Mensa, 2015; Visser et al., 2015). Therefore, the findings from this study would call for the current knowledge gaps to be addressed by conducting studies that would consider the possibility of counterfeit and substandard medicines in areas of the world with limited scientific research published on the matter, such as the Middle East, the selection of non-communicable disease medicines as a therapeutic class for investigation and conducting chemical analysis test of the API, in addition to source authentication and package inspection.

The next part of this study addressed the issue of limited published scientific research pertaining to counterfeit and substandard medicines through laboratory testing of medicine samples in the Middle East and scarce evidence worldwide regarding medicine authentication of source and package inspection of non-communicable disease medicines. Glibenclamide, a popular antidiabetic medicine, was therefore selected on these bases, in addition to the high volume of consumption reported within the targeted healthcare setting within the MOI-MSD in Saudi Arabia (Table 6). Additional samples were also collected from community pharmacies in another city (Najran) in Saudi Arabia for comparison purposes. The chemical analysis of glibenclamide samples was performed using HPLC to confirm the API quantity of glibenclamide according to USP (36) pharmacopoeial specification. The authentication of glibenclamide source was performed by examining official reception documents with samples obtained only from the MOI-MSD (Appendix 8). Packaging inspection was performed by using a tool kit developed by WHPA and FIP for the visual inspection of medicines (FIP, 2013). The results of this study indicated that all glibenclamide samples were within the accepted USP (36) limits in terms of quantity. This finding is not in line with results from previous chemical analysis tests of amoxicillin samples in Saudi Arabia which found samples with unacceptable API limits (Kyriacos et al., 2008; Khoja et al., 2013a). However, these results were similar to a study conducted on another antidiabetic medicine (metformin) in Saudi Arabia that found the correct quantities of the API according to USP specifications (Afifi & Ahmadeen, 2012). Moreover, the source of glibenclamide samples from MOI-MSD settings was authenticated by comparison with official reception documents. Visual analysis of package information revealed no signs of errors or noticeable defects. It was, therefore, concluded that the MOI-MSD glibenclamide samples collected in this study were up to the required standards in terms of API quantity, were authentic in terms of source and had no visual defects by package inspection. Thus, it was necessary to examine the quality of medicines and any related problems from a social paradigm, by examining the MOI-MSD stakeholder's perceptions about these issues in the next part of this study.

The following part of this study aimed at documenting published research on the topic of stakeholders' perceptions about medicine quality and any related problems, such as counterfeit and substandard medicines. A detailed review of such evidence was not available and therefore this part of the study addressed this knowledge gap by conducting a systematic review of the literature regarding stakeholders' perceptions about medicine quality and any related problems. It was found that a good quality medicine was defined in terms of effect by patients (Syhakhang et al., 2004; Patel et al., 2010; Patel et al., 2012), nurses (Syhakhang et al., 2004), pharmacists and physicians (Patel et al., 2012). Good quality medicines were also perceived as being expensive medicine from well-known manufacturers by some patients (Syhakhang et al., 2004). As for counterfeit medicines, commissioners in the public sector defined them as medicines that entered the country illegally and did not conform to the required specifications (Alfadl et al., 2013) while commissioners from the private wholesaler industry reported a wide range of characteristics of a counterfeit medicine including unregistered medicines, fraudulent manufacturing, had lower quantity of API and expired medicines (Khan et al., 2011). Perceptions about medicine quality were high in the opinion of patients (Syhakhang et al., 2004) and healthcare providers, including nurses, pharmacists and physicians (Syhakhang et al., 2004; Patel et al., 2012). This would indicate high trust by patients and healthcare providers in the quality of medicines in a country, regardless of the absence of scientific literature indicating medicine quality problems such as is the case with South Africa, or the presence of such evidence in Laos as noted in a previous part of the study (Chapter 3). It should also be noted that perceptions of generic medicines as being of poor quality have been found among physicians (García et al., 2011; Dunne et al, 2014a) and patients (Patel et al., 2010; Patel et al., 2012; Dunne et al, 2014b). Such perceptions could also extend to perceiving generic medicines as being counterfeit on the part of some patients (Håkonsen & Toverud, 2011; Patel et al., 2012). Moreover, practices to ensure medicine quality were only identified in two studies (Patel et al., 2009, Khan et al., 2011). Commissioners in South Africa procured medicine from licensed suppliers, and used standard operating procedures and audits as strategies to ensure medicine quality in their settings (Patel et al., 2009). Executives from the wholesaler level in Cambodia used registration information, credibility of product and reputation of manufacturer as

key characteristics to ensure the quality of medicine at the procurement level and used visual analysis of medicine consignments to check for intactness and product information as key strategies to ensure quality of medicines at the reception level (Khan et al., 2011). However, none of the identified studies have explored the healthcare providers' practices to ensure medicine quality and none have investigated practices to ensure medicine quality during the storage and transportation of medicines. In addition, several barriers to practices to ensure medicine quality were identified in some studies. Lack of communication regarding medicine quality problems by pharmacists and commissioners (Law & Youmans, 2011; Patel et al., 2009), lack of knowledge about the methods to report medicine quality concerns on the part of nurses, physicians and patients (Binkowska-Bury et al., 2012a; Binkowska-Bury et al., 2012b), low practice levels to ensure medicine quality on the part of pharmacists (Shahverdi et al., 2012), limited resources to track and lenient penalties for offenders in the opinion of pharmacists (Law & Youmans, 2011) were all identified as key barriers to ensuring medicine quality by healthcare commissioners and providers. Therefore, it was necessary to conduct a study that addresses the multiple knowledge gaps regarding medicine quality and any related problems from various stakeholders' perspectives, in conjunction with considering a different setting from what has been already explored, in order to enhance knowledge about a topic where little has been established so far. The next part of this study addressed these issues from the perspectives of commissioners, physicians, pharmacists and patients in a previously unexplored country: Saudi Arabia.

The final part of this study explored the perception of various stakeholders in MOI-MSD settings in Saudi Arabia regarding medicine quality and any related issues. The results were triangulated in order to find common themes and/or differences in opinions regarding the topic among the healthcare commissioners, providers and patients in these settings.

The definition of a good quality medicine was largely focused on its perceived effects, rather than the technical features of a medicine, in the opinion of commissioners, physicians, patients and, to a lesser extent, pharmacists. Such an understanding of medicine quality in terms of desired effects has been previously reported by different

stakeholders in previous studies (Syhakhang et al., 2004; Patel et al., 2010; Patel et al., 2012). Surprisingly, many pharmacists from both the commissioner' and healthcare provider' groups defined a good quality medicine as a medicine from a reputable, innovative pharmaceutical company. This would suggest that pharmacists in this study associated brand medicines with better quality more than did other stakeholders in this study. It has been previously suggested in the Saudi Arabian media that patients have a tendency to prefer brand medicines (Abdullah, 2013), possibly because of the limited trust they have in generic medicines manufactured in developing countries. However, the results of this study suggest that pharmacists held these beliefs also and these were expressed on more occasions. A possible explanation of such findings can be found within the pharmacists' views in this study, where commissioners associated generic medicines with quality defect warning letters received from the SFDA, while pharmacists in primary clinics associated generic medicines with previous medicine quality defects which had been visually noticed in their practice. Another surprising result was the limited reference to the registration status of a medicine with the SFDA as a characteristic of a good quality medicine among all stakeholders in this study. This result contrasts with previous studies which reported that commissioners from both public and private pharmaceutical sectors in other countries emphasised pharmaceutical product registration as a key determinant of a medicine's quality (Alfadl et al., 2013; Khan et al., 2011). Perhaps there is limited knowledge, awareness or trust among stakeholders in this study regarding the medicine registration processes performed by the SFDA in the country. It is also possible that current medicine registration processes failure in reducing the prevalence rates of counterfeit and substandard medicines according to the findings of a recent systematic review could have affected their opinion (El-Jardali et al., 2015). Moreover, it was surprising to find that only a few stakeholders, primarily from the pharmacists' group, have indicated visual characteristics of a medicine as a possible measure for medicine quality. Visual analysis of a medicine's appearance, packaging and information can be a tool to determine medicine quality problems, with limited or no resources required, as observed in a previous part of this study (Chapter 3).

Similarly, the stakeholders in this study also defined a counterfeit medicine as a medicine with no or little effect. This result was in contrast to previous studies, which suggested that commissioners in a developing country described a counterfeit medicine as an illegally sourced medicine (Alfadl et al., 2013). This also contrasts with the WHO definition of a counterfeit medicine, which emphasises the product identity and the source as key indicators of a counterfeit medicine (WHO, 1999a). Limited knowledge about counterfeit medicines could be associated with their confusion with generic medicines or expired medicines, as was shown by some patients and physicians in this study. The literature has reported supporting evidence of patients' perceptions about generic or expired medicines being counterfeit (Sarradon-Eck et al., 2007; Håkonsen & Toverud, 2011).

Furthermore, limited knowledge about medicine names was found among one-quarter of the patients who participated in this study. A previous study in Saudi Arabia has reported that community pharmacists in the Eastern part of the country had estimated that one-third of patients in their settings brought empty medicine bottles or boxes since they had no knowledge of their medicines' names (Khan & Ibrahim, 2012). This is particularly alarming with chronic patients in this study, where one-third of them did not know their medicines' names, despite the fact that they should be using them regularly. A number of possibilities could explain this finding, such as the limited education they receive regarding their medicines, regular changes to the medicines they receive because of annual medicine tenders which makes remembering all the brand names difficult, or poly-pharmacy where patients co-administer many medicines due to multiple co-morbidities. Patients' having no knowledge about their medicines' names, combined with other issues such as medicine non-availability, which has also been reported in this study, could increase the risk posed to patients in not administering the correct medicine or administrating two similar medicines for the same condition, and thereby increasing the risk of medicine-related toxicity. Patients co-administering two similar medicines due to lack of knowledge has been previously reported in some studies with Pakistani chronic patients in Norway (Håkonsen & Toverud, 2011).

A common belief among most members of all stakeholder' groups was that the quality of medicines in Saudi Arabia was high. However, less confidence among MOI-MSD staff was shown in the quality of medicines available within MOI-MSD settings, particularly on the part of pharmacists in both the commissioner' and healthcare provider' groups. This result could be explained by the pharmacists' protective views about their role as guardians of medicines (Alhamarnah et al., 2011), quality defect letters they receive from the SFDA concerning generic medicines or their negative experiences with the quality of some medicines based on previous visual inspections. Indeed, pharmacists' low opinions on the quality of medicine within the MOI-MSD could have been associated with a negativity bias which favours remembering negative experiences rather than the positive experiences in their prolonged engagement with medicines (Rozin & Royzman, 2001). Surprisingly, patients in this study demonstrated more trust in the quality of medicines in the MOI-MSD when compared with other stakeholders. Possible explanations for this result could be successful healthcare professionals' interventions at the MOI-MSD to prevent questionable quality medicines from reaching patients or that patients may not question the quality of medicines which they receive free of charge, despite previous studies in South Africa which have suggested that some patients may perceive free medicine as being of inferior quality (Patel et al., 2010).

Another common belief among all stakeholders, particularly pharmacists, was that higher priced medicines guaranteed a higher quality product. This belief could be associated with brand loyalty (Grabowski & Vernon, 1992; Costa-Font, Rudisill & Tan, 2014), since innovator brand products are introduced earlier in the market and therefore any subsequent generic product would most likely have a cheaper price. This, in turn, would be related to negative experiences which pharmacists encountered with some generic medicines, as previously discussed, to develop such beliefs. It could also be possible that such beliefs were related to the assumption that developed countries manufactured better quality medicines than developing countries, as demonstrated by different members of the stakeholder' groups. Such beliefs have been previously reported by patients in the Saudi Arabian media (Abdullah, 2013). However, the patients in this study were found to have a unique belief that the quality of medicines

differs between hospitals in Saudi Arabia. This belief could have been associated with their visits to different hospitals, where they received different medicines for the same medical condition, due to different procurement practices among healthcare sectors within the country. This would suggest, however, that patients might question the quality of a medicine when the medicine brand names change frequently.

All stakeholder groups in this study estimated counterfeit medicines to be widely prevalent worldwide as well as in Saudi Arabia. More than two-thirds of the members of each stakeholder group estimated that counterfeit medicines have more than a 10% prevalence rate on a global level and in Saudi Arabia. These estimations exceed regulatory agencies' estimation of 10% or less globally, issued by the WHO (Cockburn et al., 2005; Heyman et al., 2011; Ziance, 2008) and by the SFDA in Saudi Arabia (Arabnews, 2010). However, this estimation would more likely demonstrate a lack of knowledge about medicine counterfeiting rather than genuine concerns about medicine quality, which was generally perceived by stakeholders as being high in Saudi Arabia, as previously discussed. Therefore, caution is advised when asking stakeholders about their estimation of counterfeit medicine prevalence rates without establishing their knowledge about counterfeiting in advance.

The source of information regarding medicine quality and any related issues could be a key factor in shaping beliefs about them. Within the context of this study, the stakeholders had different sources of information for knowledge about medicine quality and any problems. Commissioners emphasised SFDA warning letters about medicine quality defects, while healthcare providers focused on actual experiences with medicine use. On the other hand, patients generally sought the advice of the physician to provide them with the necessary information pertaining to medicine quality. Surprisingly, very few patients have identified the pharmacist, who is the dispenser of the medicine, as a source of information about medicine quality and any other related problems. This led the researcher to explore the healthcare providers' views on the role of the pharmacist in MOI-MSD settings in the final part of this study. It was found that pharmacists' roles were perceived mainly as dispensing medicines and providing information related to medicines to medical staff and patients. However, it was also found that certain barriers,

such as lack of space and time to counsel patients, could limit the pharmacists in MOI-MSD settings from fulfilling their responsibility to educate patients about their medicines and, therefore, could have limited the strength of relationship between pharmacists and patients in MOI-MSD settings. On the other hand, equal emphasis should be given to increasing the pharmacist's trust in the quality of medicines they dispense within the MOI-MSD, as well as strengthening the patient-pharmacist relationship in order to avoid the transfer of negative perceptions about medicine quality from the pharmacists to the patients, which could result in medicine non-adherence and the wasting of scarce resources.

Most commissioners in this study believed they had encountered medicines of questionable quality in their practice in MOI-MSD settings. In contrast, healthcare providers largely did not report such encounters, particularly from within the physicians' group. It is possible that the nature of physicians' work in diagnosing medical conditions and prescribing medicines could have limited their exposure to questionable quality medicines. Patients' opinions resulted in half of them agreeing that they had previous experiences with questionable quality medicines while the other half did not report any such experiences. Most stakeholders' experiences, except the pharmacists, reported incidents where medicines were not effective. Such experiences could have resulted from other issues besides medicine quality, such as incorrect diagnosis, antibiotic resistance or other reasons. On the other hand, pharmacists identified several experiences which could be related to medicine quality defects, such as appearance or odour problems, medicines with no stated expiry date or medicines with less than the stated dosage numbers. This result demonstrates that medicine quality problems do probably occur in the MOI-MSD settings and are likely to be accurately identified by pharmacists in primary clinics.

Stakeholders' behaviour when in doubt about medicine quality varied considerably between the different groups. Commissioners and pharmacists were more concerned about reporting such concerns to the higher authorities including the SFDA. In contrast, physicians and patients were more concerned with stopping prescribing/using the medicine with questionable quality. However, reporting such concerns about medicine

quality was a major barrier to practice as reported by members from all stakeholder' groups. It appears that a recognised mechanism to report such medicine quality concerns was not known by healthcare providers, despite the existence of such reporting forms within MOI-MSD settings (Appendix 24). Limited knowledge about the mechanism of reporting medicine-related problems, such as adverse drug reactions, have been previously reported in different cities in Saudi Arabia (Bawazir, 2006; Khan, 2013; Al-Hazmi & Naylor, 2013; Abdel-Latif & Abdel-Wahab, 2015) and worldwide (Suyagh et al., 2015; Aziz, Siang & Badarudin, 2007). Another possible limitation to the reporting of medicine-related problems in this study was that reporting forms appear to be directed to the Pharmacy and Therapeutic Committee within the MOI-MSD. Committees, however, may not have adequate time and resources to increase knowledge about medicine quality and to improve the reporting of such issues, compared with a specific department which could implement such activities in their daily work.

Stakeholders, particularly pharmacists and physicians, reported a wide degree of scepticism regarding the quality of medicine supply activities such as medicine selection, procurement, storage and transportation conditions. The medicines available within the MOI-MSD were often described as being outdated and in need of improvement. However, in such limited resource settings, guidance from international organisations, such as the WHO, could be beneficial in selecting the most cost-effective and essential medicines (WHO, 2015). Therefore, cross-checking the medicines available in the MOI-MSD formulary with the WHO essential list of medicines and then communicating these results to the physicians and pharmacists could improve their confidence in the medicine selection processes.

The procurement of medicine was commonly described as being price-dependent rather than quality-dependent. This could be true of similar medicines which are registered with the SFDA and which would only compete based on price since the available Saudi Arabian governmental procurement regulations would favour the selection of local and cheaper products (MOF, 2006). Also, patients in this study, particularly from outside the capital, Riyadh, have reported problems with the availability of medicine in primary care clinics, which resulted in them acquiring the required medicines from elsewhere

and this was commonly described as expensive by the patients. This could indicate the need to improve the medicine procurement processes in these settings, as this would probably result in financial burdens for patients, in addition to exposing them to medicines from unknown sources. Possible improvements to the procurement practices could be achieved by implementing a system to collect data in order to evaluate suppliers' performance, including delivery history and previous quality problems associated with their products (WHO, 2007). Such data could then be used, in addition to the governmental regulations regarding the price, in order to improve medicine procurement practices. Another possible improvement to procurement practices could be achieved by establishing a local MOI-MSD tender for medicines, which would focus on chronic medicines which are frequently demanded by regular patients, in order to avoid medicine non-availability issues which could be associated with joint procurement programmes because of their commitment to large quantities of medicine orders within different healthcare sectors. It has been previously suggested that hospital medicine tenders should focus on medicines which are most used by the patients and/or expensive items, in order to achieve immediate financial savings (Milovanovic, Pavlovic, Folic & Jankovic, 2004).

Furthermore, the MOI-MSD medicine storage and transportation conditions were often described by healthcare providers as inadequate, particularly with regard to rural areas within the country. A future observational study would be needed to further explore this issue on site, since available evidence has shown the existence of medicine storage problems in community pharmacies in Riyadh (Khoja et al., 2013a). However, some cost-effective measures could be implemented immediately, in order to ensure the quality of these practices, such as including batch quality certificates for each medicine received by the MOI-MSD at the main warehouse, keeping records of warehouse temperatures regularly, regular pest control of all warehouses in the country, providing reliable vehicles to transport medicines, transporting medicines with thermometers to ensure appropriate temperature control in accordance with international guidelines and standards (WHO, 2003b; DELIVER, 2003; WHO, 2007).

The stakeholders, particularly from the healthcare provider group, raised concerns and recommended the improvement of medicine monitoring and medicine analysis in MOI-MSD settings. They largely perceived that the task of medicine analysis should be performed by the SFDA and that the MOI-MSD should frequently send medicine samples for periodic analysis. This could be true, since the available evidence in this study does not support the notion of allocating scarce resources to establish laboratories in the MOI-MSD settings. On the other hand, this may require that a national framework would be developed and implemented in order for the SFDA to have legal authority to investigate and collect samples on site from all public healthcare organisations such as the MOI-MSD in addition to their current practices that focus on analysis of medicines in the country ports or from private healthcare organisations or pharmacies. Furthermore, international guidelines support conducting random sample checks where possible, in order to investigate the quality of medicines at the post-procurement end of the medicine supply chain (WHO, 2007). However, the SFDA only has one laboratory to test medicine quality in the entire country. Therefore, a practical consideration needs to be taken into account, where only questionable quality medicines, based on observation or signals from patient' or healthcare providers' complaints, would be sent by the MOI-MSD to the SFDA for further investigation. It could also be possible for the MOI-MSD to use existing technologies such as handheld NIR or Raman instruments to screen the quality of medicine samples and address issues of temperature or humidity at the end of the supply chain cycle before they are dispensed to patients. A recent systematic review of the literature has found that both portable NIR and Raman devices are suitable for ensuring medicine quality in low-resource settings in terms of cost, personnel training required and the diminished need for laboratory supplies, electricity power or designated facilities (Kovacs et al., 2014).

Additionally, healthcare providers and patients had perceived inadequate medicine monitoring as a barrier to medicine quality within the MOI-MSD. Medicine monitoring is ideally relevant throughout all of the medicine supply cycle, including procurement, reception of medicines and medicine storage and/or transportation according to international guidelines (DELIVER, 2003). Based on these guidelines, several steps could be implemented in order to ensure medicine monitoring and, therefore, possibly

improve the stakeholders' perceptions about them. At the procurement stage, monitoring could include previous patients' complaints about specific pharmaceutical products and/or suppliers through a reporting system, monitoring direct and indirect costs related to medicines, in addition to suppliers' adherence to delivery schedules. At the reception stage, monitoring could include checking batch quality analysis certificates and the conformation of the received medicine with the purchase order. At the storage and transportation stage, monitoring could include measuring temperature and humidity regularly to ensure adequate conditions, according to the manufacturer's specifications, and keeping these records for future review.

8.1 Summary

What is already known about this topic:

- Medicine quality problems such as counterfeit and substandard medicines are increasing worldwide and could affect health, the economy and patient' trust.
- All stakeholders in developing countries could believe that a good quality medicine may be identified through its perceived effect. Patients also believed that higher priced medicines and reputable manufacturers represent a good quality medicine. Commissioners defined a good quality medicine in terms of good medicine manufacturing, storage and distribution conditions.
- Commissioners in Sudan and Cambodia defined a counterfeit medicine as a medicine illegally entering a country with unacceptable specifications, unregistered, fraudulently manufactured, or with low API, as well as expired medicine.
- Healthcare providers (i.e. nurses, pharmacists and physicians) and patients in developing countries perceived that the quality of medicines was high in their own settings.
- Physicians, pharmacists and patients in developing and developed countries could have views that generic medicines are of poor quality. Patients in developing countries may also believe that generic medicines are counterfeit.
- Commissioners' practices to ensure medicine quality in Sudan and Cambodia included supply from licensed suppliers, using standard operating procedures, performing audits, ensuring medicine registration status, considering

manufacturer and product reputation at the procurement level. They would also conduct visual inspection of product intactness and information during reception of the medicine consignment.

- Barriers to practices for medicine quality assurance could include lack of knowledge of the method to report medicine quality problems, in the opinion of healthcare providers (nurses and physicians) and patients in developing countries. Pharmacists and commissioners also reported lack of communication between healthcare staff, as being a barrier to ensuring medicine quality. The pharmacists have also identified low practice levels in addressing this issue, limited resources and lenient penalties for offenders, as possible barriers to the practices required to ensure medicine quality in developing and developed countries.

What this study adds:

- Systematically demonstrated that the majority of medicine quality problems reported in the field quality surveys in the literature were of substandard medicines, having out of specification API amounts, rather than being counterfeit.
- The majority of laboratory-based medicine quality surveys in the literature were conducted on infectious disease medicines and not widely used chronic medicines or clinically significant narrow therapeutic medicines.
- Only two studies investigating counterfeit and substandard medicines in laboratory settings were found in the Middle East and none in Saudi Arabia at the time of the systematic review of the literature. Since then, an additional study was performed to chemically analyse amoxicillin samples from private pharmacies in Saudi Arabia.
- The systematic review of the literature identified that only 10% of included research articles had conducted chemical analysis of samples, authentication of medicine source and package inspection simultaneously to account for the possibility of counterfeiting in the selected samples.
- The quality of glibenclamide collected from MOI-MSD settings in Saudi Arabia was found to be acceptable in terms of API quantity according to USP

specifications; source authentication was confirmed through official reception documents and packaging information revealed no signs of concern.

- It was possible to use social media tools such as WhatsApp to distribute survey questionnaires in settings that use them as a mode of communication between administrations and staff, for example.
- Commissioners, healthcare providers and patients in this study have also largely identified a good quality medicine in terms of effect, similar to previous studies conducted in medium or low-income countries.
- Healthcare providers, commissioners and patients in this study mostly identified counterfeit medicines from their perceived effect. Laboratory specifications such as the presence of the correct API and medicine package information were predominantly identified by some pharmacists in this study. Only a few pharmacists and physicians from the healthcare provider' group specified that counterfeit medicines originate from an unreliable source. This result could explain why the majority of all stakeholders in this study estimated the prevalence of counterfeit medicines in Saudi Arabia and worldwide higher than any official estimation.
- Some physicians shared the views of some patients in this study where a counterfeit medicine was identified as a cheaper generic medicine, an inadequately stored or expired medicine.
- While the majority of stakeholders believed that the quality of medicines was good in Saudi Arabia, less confidence was shown in the quality of medicines in the MOI-MSD settings, particularly by pharmacists.
- The majority of MOI-MSD stakeholders' perceived experiences with questionable quality medicines were concerned with limited medicine effect, which cannot be related to medicine quality problems only. A few pharmacists reported experiences that could be related to medicine quality problems such as medicine appearance, taste or odour defects.
- Commissioners have shown that SFDA warning letters could have a negative impact on their confidence about the quality of generic medicines. Patients, on the other hand, particularly chronic patients, appear to be influenced by their physicians' opinion about medicine quality in MOI-MSD settings.

- The healthcare providers (pharmacists and physicians), commissioners and patients recommended improvement to medicine monitoring, medicine analysis, reporting of medicine quality problems, the medicine procurement system and medicine storage conditions, in order to ensure the quality of the available medicines within the MOI-MSD. The healthcare providers have also suggested improving medicine selection in the local formulary, medicine transportation conditions and establishing a medicine quality department or committee to ensure medicine quality.
- This study has shown several difficulties which MOI-MSD patients' encounter in their primary clinics, particularly patients located away from the capital, Riyadh. Such challenges included medicine non-availability, high medicine prices, limited knowledge about their medicine names, remote clinic locations and short opening times, which could lead to extra financial burdens on patients, place them in unnecessary threat from medicines with unknown sources or lead to patients' non-adherence to their medicine regimens.

8.2 Conclusion

The results of this study indicated that the quality of glibenclamide collected from MOI-MSD settings and from community pharmacies were within API pharmacopoeial specifications and with no visual signs of defect in the tablets or their packaging. Furthermore, the glibenclamide samples collected from MOI-MSD settings were authenticated in terms of source by comparing them with official medicine reception documents. This would suggest that the SFDA prevalence estimation of counterfeit medicines in Saudi Arabia might be accurate, in contrast to media predictions. However, perceptions about medicine quality and any related issues were found to be a cause for concern. Most stakeholders believed that good quality and counterfeit medicines could be identified based on effect rather than laboratory testing, authentication of source or visual inspection. These beliefs demonstrated severe lack of knowledge about medicine quality and any related issues, when compared with existing evidence in the literature about counterfeit and substandard medicines. Although the majority of stakeholders expressed confidence in the quality of medicines in Saudi Arabia, this was not always the case with medicines in the MOI-MSD, particularly with pharmacists. The reasons for pharmacists' scepticism about the quality of medicines in the MOI-MSD could be associated with their prolonged engagement with medicines in their role, previous negative experiences with generic medicines, SFDA warning letters predominantly about generic medicines or their belief that higher priced medicines would guarantee better quality. Behaviour, when in doubt about medicine quality, varied considerably among stakeholders, which would suggest the absence of an agreed and known method for reporting such concerns. Pharmacists, more than other stakeholders, recognised the importance of communicating such concerns to higher authorities, including the SFDA. The stakeholders identified medicine monitoring, medicine analysis, procurement practices, medicine storage conditions and reporting medicine quality problems as areas for improvement to ensure medicine quality in their settings. Furthermore, this study has identified several patient-related issues such as medicine non-availability, high medicine prices, the remote location of primary clinics and their short opening times, which could result in financial burdens on patients, make them vulnerable to medicines from unknown sources or lead to medicine non-adherence.

8.3 Practice implication

- The findings of this study suggest that medicine quality problems within the MOI-MSD in Saudi Arabia were associated with the social paradigm of perceptions about medicine quality and any related issues rather than the laboratory-based scientific analysis of medicine quality. This would suggest the need to develop appropriate intervention through educational programmes in these settings, in order to increase awareness about the definition and types of medicine quality problems.
- Pharmacists from both the commissioner' and healthcare provider' groups demonstrated the lowest degree of confidence in medicine quality in their settings, when compared with other stakeholders' perceptions. Thus, the implementation of quality assurance measures based on international guidelines in medicine selection, procurement, storage and transportation are needed in order to improve the confidence of pharmacists in medicines in their settings.
- Patients in this study, particularly female and uneducated patients, had high opinions about the quality of medicines in Saudi Arabia and within the MOI-MSD. They mostly based the information they had about medicines quality on their physician's advice. Minimal confidence was shown by patients regarding the pharmacists' advice about their medicines. This could be attributed to the pharmacists' limited patient counselling in these settings. Therefore, allocating space and time for pharmacists to counsel patients regarding their medicines is significant to improve the pharmacists-patient relationship in order for patients to have immediate access to medicine-related information by a trusted healthcare professional, which may not always be possible with physicians, who could be engaged with other patients' appointments.
- This study has identified several barriers that some patients encounter in MOI-MSD settings such as medicine non-availability, high medicine prices, limited knowledge of patients about their medicine names, distant locations of primary clinics and their short periods of opening. Such barriers could result in undesired outcomes for the patients, such as extra expenditure on procuring medicines from unknown sources or could negatively impact on their health due to medicine non-adherence. Thus, it is important that decision-makers in MOI-

MSD settings become aware of these patient-related issues, particularly healthcare providers, explore the reasons for some of these problems and design appropriate strategies to minimise or diminish such barriers.

8.4 Strength and limitations of the research

Strengths

- The major strength of this study is integrating pharmacy practice approaches to explore stakeholders' perceptions with pharmaceutical analysis of a selected high volume antidiabetic medicine (glibenclamide) to address the research question about medicine quality and any related issues in one setting.
- The study that explored stakeholders' perceptions about medicine quality and any related issues used a mixed method approach in addition to triangulation method to enhance the validity and reliability of the obtained results.
- This study investigated different stakeholders' perceptions about medicine quality and any related issues, such as counterfeit medicines, in one major governmental healthcare sector in Saudi Arabia, including commissioners (decision-makers), pharmacists and physicians (healthcare providers) and patients (users).
- To the researcher's knowledge, this study was the first to combine perceptions about medicine quality and counterfeit medicines. In addition, this study was the first to comprehensively explore the differences and similarities of medicine decision-makers, providers and users regarding the research issue in one setting in Saudi Arabia.
- The systematic reviews in this study (Chapter 3 and 5) identified gaps in knowledge that were utilised to inform the aims and objectives in this study, as well as to encourage researchers worldwide to conduct research studies in the relevant fields accordingly.

Limitations

- The analysis of glibenclamide samples focused on API quantities based on the findings in the systematic review regarding the most common problems relating to medicine quality available in the literature and the types of analysis

performed (Chapter 3). Therefore, this study did not investigate the API identity, excipients in the samples, physical properties or use other analytical tools such as MS or NMR to identify the structure of the contents due to their complex nature and the limited time available.

- The sample size in the laboratory phase and the stakeholders' perception phase of the study could be considered small due to location constraints and time limitations. However, the sample size calculation in both phases was based on recognised methods and was comparable with many studies from both fields.
- The study of the perception of stakeholders regarding medicine quality and any related issues was exploratory in nature and therefore focused on semi-structured interviews, to shed light on the relevant issue where little is known, rather than to attempt to generalise findings.
- The selection of stakeholders in this study was based on the medicine supply cycle within the MOI-MSD to involve medicine supply decision-makers, prescribers, dispensers and users. However, the perceptions of other stakeholders, such as nurses or healthcare technicians, for example, were not explored because they were beyond the scope of this study.

8.5 Recommendations

The threat of medicine quality problems such as counterfeit and substandard medicine is evident and could occur in any country regardless of the strength of their regulatory systems. On the other hand, negative perceptions about the quality of medicines without sufficient and scientific evidence to confirm them could lead to the wasting of scarce financial resources and inaccessibility to acceptable quality medicines which could, in turn, have harmful effects on the patient's health. The findings suggest that the actual quality of medicines was acceptable and the majority of patients were satisfied with them. However, the medicine supply commissioners and healthcare providers, particularly pharmacists, were more sceptical about the quality of medicines in their own settings. Therefore, improving healthcare staff confidence about the quality of medicines available within the MOI-MSD through educational campaigns, ensuring quality in the different stages and processes of the medicine supply cycle and improving communication, would be the basis of the recommendations of this study as follows:

- The relationship between the MOI-MSD and the medicine regulatory agency in the country (SFDA) should be improved in order to ensure timely responses to medicine quality concerns and to expose healthcare commissioners and providers to the SFDA methods of ensuring medicine quality, in order to improve their confidence via site visits, if possible.
- Reporting of medicine quality or other medicine-related concerns could be improved by designating the task of exchanging such information between the MOI-MSD and the SFDA to a specific department within the MOI-MSD rather than to a committee that cannot commit daily tasks to collect, follow-up and exchange such information. The reporting of such problems could also be improved by field visits of this designated department to primary care clinics and providing various methods to report medicine-related concerns to all stakeholders such as telephone, fax, e-mail or social media.
- Medicine selection in the MOI-MSD formulary could be compared with what is available in the WHO essential medicine list or other treatment guidelines, such as The National Institute for Health and Care Excellence (NICE) guidelines, and the information would then be communicated back to healthcare commissioners and providers to increase their confidence.
- Implementing a system to evaluate medicine suppliers' performance by collecting data about medicine direct and indirect costs, delivery date adherence and previous medicine quality complaints, and then implementing these data in the medicine procurement decisions, could further increase the confidence of stakeholders about the quality of medicines within the MOI-MSD.
- Including a certificate of quality analysis for each batch of medicine delivered to the MOI-MSD by various suppliers could ensure the quality of each medicine consignment and improve perceptions about their quality.
- Measuring and recording of temperatures during medicine storage and transportation in accordance with the manufacturer's specifications could also improve perceptions about medicine quality.
- Allocating space for patient counselling in each MOI-MSD primary clinic could improve interaction with patients and, therefore, provide reliable information to patients and could increase the confidence of pharmacists in their role, which

could then be reflected towards their confidence in the medicines available in their settings.

- Educational campaigns are needed to raise the awareness of all stakeholders about the evidence and nature of medicine quality problem worldwide. This could benefit them in identifying medicine quality concerns more accurately and possibly limit the degree of unnecessary concern regarding medicine quality, without sufficient reasons for doubt.
- Extending the role of SFDA to investigate the quality of medicines in public health organisation settings in Saudi Arabia and the use of portable NIR or Raman devices could be essential to rapidly ensure the quality of medicines at different supply chain levels and possible issues associated with humidity and high temperatures in the country.

8.6 Further research

- The researchers are encouraged to examine the quality of medicines prospectively in terms of pharmacopoeial specifications, source authentication and package information, particularly in areas where little is known in terms of therapeutic category, such as chronic medicines and narrow therapeutic index medicines, or in terms of exploring the quality of medicines in pharmaceutical markets which have been rarely explored, such as the Middle East.
- Perceptions of stakeholders about medicine quality and any related issues, such as counterfeit medicines have been rarely addressed within the literature and, therefore, future studies to examine these perceptions from different perspectives in different settings is encouraged in order to develop and validate tools for measuring such perceptions, as they could negatively affect accessibility to acceptable quality medicines and/or waste limited resources.
- Studies exploring the perceptions of the SFDA, pharmaceutical companies and/or other healthcare sectors in Saudi Arabia, with the exception of the MOI-MSD, does not exist and therefore the researchers in Saudi Arabia are encouraged to explore the perceptions of these stakeholders in order to generate a country-wide perception, which could be beneficial in constructing national policies to address common barriers.

- Within the context of the MOI-MSD, observational studies are recommended to examine the medicine storage and transportation conditions in different primary clinics based on the results found in this study. It would also be important to examine prescribing and dispensing practices in order to explore possible association with complaints about limited medicine effects, as reported by stakeholders in this study. Furthermore, future research in these settings could examine patients' adherence to their medicines and rational use of medicines in order to generate knowledge about the complete medicine supply cycle within the MOI-MSD.

8.7 Reflection on the research process

Reflexivity can be an important part of conducting qualitative research. It entails critically examining the researcher's role and relationship with the research study and environment. Such examination could include previous preconceptions held by the researcher and how they shaped the research questions or the dynamics in the relationship between the researcher and the respondents.

My educational background and personal work experience with the MOI-MSD had, no doubt, a major influence on the shaping of this study. I have had past experience with patients and healthcare professionals complaining about the medicine quality in these settings. This may have been the most important factor for myself: to find out if such negative perceptions could be warranted. My previous work experience could have helped me identify the key commissioners to interview and, as a result, their agreement to participate in this study. As for patient interviews, every attempt was made by myself not to influence their opinions, if they had a suspicion that I worked for the MOI-MSD. I introduced myself as a researcher for UH in the UK to all patients. Nevertheless, wearing my Saudi clothing could have been interpreted by some patients as being a person of authority in these settings, particularly where their own doctors would most probably be expatriates. In a later stage of interviews with pharmacists and physicians, it came to my attention that some participants might have thought that I would be upset if I heard negative comments from them, given my previous work experience. I reminded them that all comments are welcome and would be held in confidentiality.

The study started with a literature review and protocol development stage in the first year of study. This part was essential to gather information about medicine quality problems and perceptions about medicine quality from the relevant literature. It was very beneficial for me to increase my understanding about the subject of medicine quality problems such as counterfeit and substandard medicine and discover the controversy of such issues that starts from the very definition of these phenomena from the perspective of different countries and scholars. It was also noted that no systematic reviews on the subject were available, which would be of great importance to the subject at hand and had influenced my decision to conduct it by the end of my first year of study. Furthermore, this part of the study introduced me to literature examining the technical and laboratory analysis studies on counterfeit and substandard medicines, which I found new and exciting to read although sometimes challenging since I had no prior experience of this field. Nevertheless, by the end of the first year, I was able to gain sufficient knowledge to prepare a protocol for this PhD study and to prepare a draft for the systematic review. The protocol was sent to the relevant University of Hertfordshire Ethics Committee for their approval, which was granted at the end of the first year, and a similar letter of acceptance was granted by the Ministry of Interior Medical Services in Saudi Arabia to conduct the study at their settings. Consequently, the first phase of this study started with a focus group discussion with experienced Saudi Arabian pharmacists conducting their postgraduate studies at UH at that time to help develop questions for the upcoming interview and questionnaire studies. The focus group study was a great experience for myself to practice communication skills for later interview studies and had very useful information to be utilized in the question development for the later studies, in terms of experiences with poor quality medicines, emerging issues not covered in other literature and the accepted Arabic translation of technical terms, such as counterfeit medicines, to be used later when conducting interviews with patients in Arabic. However, the focus group study did demonstrate for me the difficulty of arranging convenient group meetings with different individuals since everyone has different commitments and preferred times. It also gave me some experience in moderating such group meeting to try to balance the meeting and give everyone a chance to express his or her opinion freely with minimal peer pressure.

The second year of the study had major phases of this study including data collection and the publication of my systematic review in a scientific journal and the focus group study findings in a poster at a UH conference. Glibenclamide medicine samples were collected from the MOI-MSD general warehouse and other samples were collected from community pharmacies in Najran city for comparison purposes. At the beginning of the second year, it was necessary for me to spend a three-month period in Saudi Arabia to conduct face-to-face interviews with MOI-MSD commissioners and patients, in addition to the distribution of questionnaires to pharmacists and physicians. My physical presence in Saudi Arabia for the purpose of conducting these studies could have greatly influenced the number of participants agreeing and may have also facilitated more rapid responses for the survey questionnaire. However, it could have also affected the opinions of some patients, particularly some female patients, during the interview process by the possibility of not speaking freely due to cultural barriers in these setting between male and female individuals. It is therefore possible that female researchers could obtain more information from some female patients, particularly the ones who did not agree for the interview to be tape-recorded. It was my observation that younger and more educated female participants were more open to sharing their views and also to their agreement for the interview to be tape-recorded.

In the third and final year of the PhD study, the data collection of interviews with pharmacists and physicians in the MOI-MSD was conducted via telephone calls. This will be followed by transcription, translation and analysis of emerging themes from the interviews. In addition, ensuring the validity of translation through back translation was performed with the assistance of two native Arabic speaking members of staff at UH. Also, the write up for the final thesis was started in conjunction with this phase of the study. Between March and April 2015, my work was presented via poster presentations at UH and an International Pharmacy conference held in Germany in addition to an oral presentation at UH. This was a great opportunity to communicate my research findings to the wider research community and meet with other researchers who share similar interests in the field. The study was concluded by examining similarities and differences between emerging themes from the various phases of the study before a complete

understanding of the research problem and findings can be reached and recommendations can be given in the final stages of the thesis.

The experience of conducting research towards a PhD qualification has been a life learning experience without a doubt. I have improved my communication skills through multiple interactions with participants while approaching and conducting interview studies. I have practiced the role of an independent researcher in research design, data collection, data analysis, data interpretation and communicating my findings to the wider community through presentations and publication of studies in scientific journals. For that, I am forever grateful to my sponsors, university, supervisors and colleagues for supporting me in achieving my objectives.

9 Research output

Publications

Alghannam AFA, Aslanpour Z, Evans S, Schifano F. OHP-024 Pharmacist focus group about quality of medicines and related issues. *European journal of hospital pharmacy*. 2015;22(Suppl 1):A203-A204.

Alghannam AFA, Aslanpour Z, Evans S, Schifano F. A systematic review of counterfeit and substandard medicines in field quality surveys. *Integrated Pharmacy Research and Practice.* 2014;3:71-88.

Presentations

Life and Medical Sciences Conference; University of Hertfordshire-14th April 2015. Survey with MOI-MSD pharmacists and physicians in Saudi Arabia regarding medicine quality and related issues.

Department of Pharmacy evening sessions; University of Hertfordshire-11th June 2014. Evaluation of glibenclamide quality: analysis and perceptions of stakeholders' about medicine quality in Ministry of Interior clinical settings.

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11 Appendices

Appendix 1: Comparison between some chemical analysis methods

Characteristic	HPLC	NIR	NMR	Raman
Identification (API and excipient)	API	All	All	All
Quantification (API and excipient)	Yes only API depending on detector	Yes	No	Yes
Time	Slow	Rapid	Rapid	Rapid
Cost	High cost in consumables and reagents	Affordable. No ongoing cost of maintenance and sample	Expensive	Affordable. Might need change of laser
Personnel Requirement	Training and knowledge required	Minimum training required	Must be experts	Minimum training required
Destructive method	Yes	No	Yes	No
Portable option	No	Yes	No	Yes
Major Attributes	Provide chemical information. Can detect impurities, adulterants or degraded substances Needs sample preparation Sensitive technique can reach Nano-gram level Can be automated to work 24 hours daily Can be coupled with MS to identify unknown samples	Provide chemical and physical properties information No or minimal sample preparation Sensitivity can reach micro-gram level (<5% m/m) Can be automated to work 24 hours daily in NIR imaging Can identify different batches of same drug Mostly no need to remove sample from package Sensitive to humidity and temperature. Can differentiate water content (difference in storage conditions)	Provide chemical structure and composition of unknown Needs sample preparation Sensitive technique can reach Nano-gram level Can detect mixtures simultaneously in a single run in DOSY NMR	Provide chemical information. Can detect aromatic bonds such as S-S and C double bonds No or minimal sample preparation Sensitivity can reach micro-gram level (<10% m/m) Can be automated to work 24 hours daily Depending on the laser type you can detect excipients as well as APIs. 1064 nm laser can identify excipients and API
Major Problems	Destructive Time consuming	Use of chemometrics Low sensitivity in samples with less than 5% m/m concentration Need a reference library of batches	Destructive Solvents are expensive	Use of chemometrics for analysis is essential Weak Raman signal can be affected by samples with high fluorescence (can be used as an advantage)

Appendix 2: Population in Saudi Arabia based on 2010 census

Region	Province	City	Population/City	Total Population
Central	Riyadh	Riyadh	5.25 million	6.77 million
		Alkharj, Aldawadmy Almajmaa, Algowaia and Wadi Aldawaser	(100,000-500,000)	
	Qassim	Buraidah	600,000	1.2 million
		Onaizah and Alras	(100,000-500,000)	
	Hail	Hail	(100,000-500,000)	597,000
Western	Makkah	Jeddah	3.4 million	6.9 million
		Makkah	1.5 million	
		Taif	980,000	
		Algonfotha and Alleth	(100,000-500,000)	
	Madinah	Madinah	1.1 million	1.77 million
		Yanbou	(100,000-500,000)	
Eastern	Eastern	Dammam	900,000	4.1 million
		Hafouf	660,000	
		Alkhobar	578,000	
		Alqatif	528,000	
		Jubail, Dhahran and Hafr Albaten	(100,000-500,000)	
Southern	Asir	Khamis Mushait	512,000	1.9 million
		Abha, Bisha, Mahail, Ahad Rofaidah, and Almjardah	(100,000-500,000)	
	Jizan	Jizan, Sabia, Abo Arish, Samta and Ahad Almasarha	(100,000-500,000)	1.36 million
	Najran	Najran	(100,000-500,000)	505,000
	Albaha	Albaha	(100,000-500,000)	411,000
Northern	Tabouk	Tabouk	569,000	791,000
	Northern Borders	Araar	(100,000-500,000)	320,000
	Aljouf	Skaka and Alqoriat	(100,000-500,000)	440,000

Appendix 3: Geographical map of MOI PCC in Saudi Arabia

Appendix 4: Sample size used in some medicine quality surveys

Reference	Number of medicines	Sample size	Ratio (sample size/ number of medicines)	Number of countries
Kenyon et al. (1999)	1	13	13	1
Shakoor et al. (1997)	5	96	19.2	2
Taylor et al. (2001)	27	581	21.5	1
Laserson et al. (2001)	3	71	23.6	6
Dondorp et al. (2004)	8	303	37.8	5
Schwertner & Storrow (2005)	5	29	5.8	2
Abdo-rabbo, Bassili & Atta (2005)	3	50	16.6	1
Gaudiano et al. (2007)	5	28	5.6	3
Kaur et al. (2008)	7	304	43.4	1
Bate, Coticelli, Tren & Attaran (2008)	7	210	30	6
Tipke et al. (2008)	6	77	12.8	1
Kyriacos, Mrouch, Chahine & Khouzam (2008)	2	111	55.5	4
Amanlou (2008)	2	23	11.5	1
Sengaloundeth et al. (2009)	1	30	30	1
Onwujekwe et al. (2009)	5	225	45	1
Hadi et al. (2010)	5	104	20.8	1
Khan et al. (2010)	3	203	67.6	1
Bate and Hess (2010)	3	339	113	2
Seear et al. (2011)	3	300	100	1
Newton et al (2011)	10	59	5.9	9
Karlage et al. (2012)	8	17	2.1	1
Stanton et al. (2012)	2	101	50.5	1

Appendix 5: Photo of glibenclamide collection in MOI-MSD

Appendix 6: Glyburide (glibenclamide) monograph USP 36

Glyburide Tablets

DEFINITION
Glyburide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of glyburide ($C_{23}H_{28}ClN_3O_5S$).

IDENTIFICATION
• **INFRARED ABSORPTION** ⟨197K⟩
Sample: Grind to a fine powder a number of Tablets, equivalent to 15 mg of glyburide. Add 30 mL of acetonitrile, and shake. Filter the mixture, evaporate the filtrate to dryness, and dry the residue in a vacuum at 60° for 3 h.

ASSAY
• **PROCEDURE**
Mobile phase: Dissolve 2.6 g of monobasic ammonium phosphate in 450 mL of water. Add 550 mL of acetonitrile, filter, and degas. Adjust, if necessary, with phosphoric acid or sodium hydroxide to a pH of 5.25 ± 0.30.
Progesterone solution: 0.2 mg/mL of progesterone in acetonitrile
System suitability solution: Dissolve 10 mg of USP Glyburide RS in 20 mL of *Progesterone solution*. Add 4.0 mL of water.
Standard solution: To 10 mg of USP Glyburide RS add 20.0 mL of acetonitrile, and shake vigorously to dissolve. Add 4.0 mL of water.
Sample solution: Transfer NLT 20 Tablets to a suitable container. Add water equivalent to 0.4 mL of water per mg of glyburide, and swirl to disperse and wet Tablet material. Then add acetonitrile equivalent to 2.0 mL of acetonitrile per mg of glyburide, and shake for 30 min. Centrifuge a portion of the suspension, and use the clear supernatant.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; packing L7
Flow rate: 2 mL/min
Injection size: 10 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for glyburide and progesterone are about 0.4 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 5.0 between glyburide and progesterone
Relative standard deviation: NMT 2.0% for glyburide
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of glyburide ($C_{23}H_{28}ClN_3O_5S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

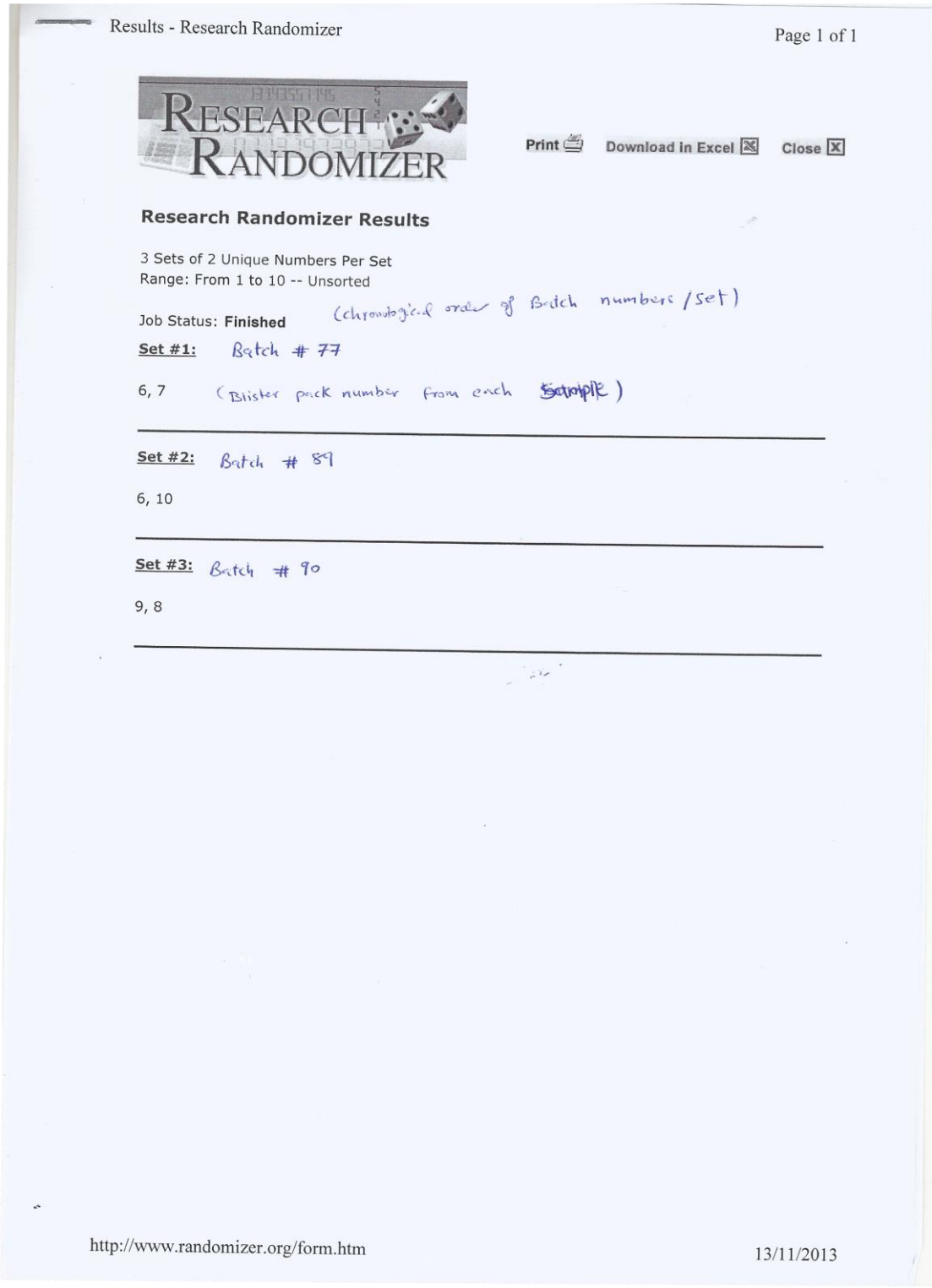
r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Glyburide RS in the *Standard solution* (mg/mL)

Time: 45 min. [NOTE—Use low-actinic volumetric flasks.]
Mobile phase: Acetonitrile and water (1:1), containing 4.0 mL of phosphoric acid per L of solution
Standard stock solution: 0.15 mg/mL of USP Glyburide RS in *Medium*. [NOTE—Sonicate for about 25 min to dissolve, and dilute with *Medium* to volume.]
Standard solutions: Dilute the *Standard stock solution* with *Medium* to obtain 0.003 mg/mL (for Tablets labeled to contain 1.5 mg), 0.006 mg/mL (for Tablets labeled to contain 3.0 mg), 0.009 mg/mL (for Tablets labeled to contain 4.5 mg), and 0.012 mg/mL (for Tablets labeled to contain 6.0 mg).
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 30-cm; 10-µm packing L1
Flow rate: 2 mL/min
Injection size: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 4000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 3.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the percentage of glyburide ($C_{23}H_{28}ClN_3O_5S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = Tablet label claim (mg)
V = volume of *Medium*, 500 mL
Tolerances: NLT 70% (Q) of the labeled amount of glyburide ($C_{23}H_{28}ClN_3O_5S$) is dissolved.
Test 2 (micronized glyburide): If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.05 M phosphate buffer, pH 8.5 (6.8 g of monobasic potassium phosphate and 1.99 g of sodium hydroxide in 1 L of water, and adjust with diluted phosphoric acid or diluted sodium hydroxide to a pH of 8.5 ± 0.05); 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Mobile phase: Acetonitrile and water containing 5 g/L of monobasic ammonium phosphate (480:520)
Standard stock solution: Transfer 67 mg of USP Glyburide RS to a 500-mL volumetric flask, dissolve in 40 mL of methanol with sonication for 5 min, and dilute with *Medium* to volume.
Standard solutions: Dilute the *Standard stock solution* with *Medium* to obtain solutions having known concentrations of 0.0017 mg/mL (for Tablets labeled to contain 1.5 mg), 0.0034 mg/mL (for Tablets labeled to

Appendix 7: Selection of random blister pack numbers in glibenclamide samples collected from MOI-MSD warehouse



Results - Research Randomizer

Page 1 of 1

RESEARCH RANDOMIZER

Print Download in Excel Close

Research Randomizer Results

3 Sets of 2 Unique Numbers Per Set
Range: From 1 to 10 -- Unsorted

Job Status: **Finished** (chronological order of Batch numbers / set)

Set #1: Batch # 77

6, 7 (Blister pack number from each ~~Sample~~)

Set #2: Batch # 89

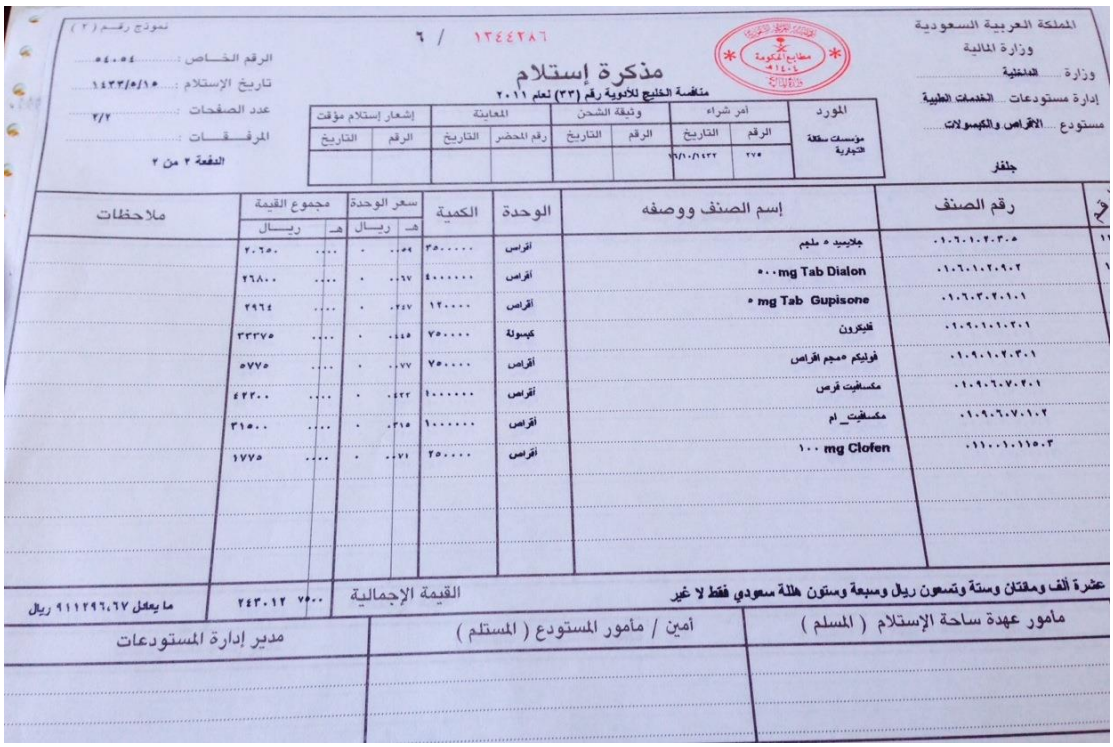
6, 10

Set #3: Batch # 90

9, 8

http://www.randomizer.org/form.htm 13/11/2013

Appendix 8: Sample of glibenclamide official receiving record



المملكة العربية السعودية
وزارة المالية
وزارة الداخلية
إدارة مستودعات الخدمات الطبية
مستودع الأقراص والكبسولات
جلفار

نموذج رقم (٢)
الرقم الخاص : ٥٤٠٥٤
تاريخ الإستلام : ١٤٣٣/٥/١٥
عدد الصفحات : ٢/٢
المرفقات :
الدفعة ٢ من ٢

٦ / ١٣٤٤٢٨٦

مطابع المكونة ١٤٠٤

مذكرة إستلام

منافسة الخليج للأدوية رقم (٣٣) لعام ٢٠١١

المورد	أمر شراء		وثيقة الشحن		المعاينة		إشعار إستلام مؤقت	
	الرقم	التاريخ	الرقم	التاريخ	رقم المحضر	التاريخ	الرقم	التاريخ
مؤسسات سقعة التجارية	٢٧٥	١٤٣٢/١٠/٢٦						

رقم الصنف	إسم الصنف ووصفه	الوحدة	الكمية	سعر الوحدة ريال	سعر الوحدة هـ	مجموع القيمة ريال	مجموع القيمة هـ	ملاحظات
٠١٠٦٠١٠٢٠٣٠٥	جلايميد ٥ ملجم	أقراص	٣٥٠٠٠٠٠	٠	٠٥٩	٢٠٦٥٠	٠٠٠٠	
٠١٠٦٠١٠٢٠٩٠٢	٥٠٠mg Tab Dialon	أقراص	٤٠٠٠٠٠٠	٠	٠٦٧	٢٦٨٠٠	٠٠٠٠	
٠١٠٦٠٣٠٢٠١٠١	٥ mg Tab Gupisone	أقراص	١٢٠٠٠٠	٠	٠٢٤٧	٢٩٦٤	٠٠٠٠	
٠١٠٩٠١٠١٠٢٠١	فليكزون	كبسولة	٧٥٠٠٠٠	٠	٠٤٤٥	٣٣٣٧٥	٠٠٠٠	
٠١٠٩٠١٠٢٠٣٠١	فوليكم ٥مجم اقراص	أقراص	٧٥٠٠٠٠	٠	٠٧٧	٥٧٧٥	٠٠٠٠	
٠١٠٩٠٦٠٧٠٢٠١	مكسافيت قرص	أقراص	١٠٠٠٠٠٠	٠	٠٤٢٢	٤٢٢٠٠	٠٠٠٠	
٠١٠٩٠٦٠٧٠١٠٢	مكسافيت_ام	أقراص	١٠٠٠٠٠٠	٠	٠٣١٥	٣١٥٠٠	٠٠٠٠	
٠١١٠٠١٠١١٥٠٣	١٠٠ mg Clofen	أقراص	٢٥٠٠٠٠	٠	٠٠٧١	١٧٧٥	٠٠٠٠	
				القيمة الإجمالية		٢٤٣٠١٢	٧٥٠٠	ما يعادل ٩١١٢٩٦،٦٧ ريال

عشرة ألف ومئتان وستة وتسعون ريال وسبعة وستون هللة سعودي فقط لا غير

مأمور عهدة ساحة الإستلام (المسلم)	أمين / مأمور المستودع (المستلم)	مدير إدارة المستودعات

Appendix 9: University of Hertfordshire ethical approval

UNIVERSITY OF HERTFORDSHIRE
Health and Human Sciences

M E M O R A N D U M

TO **Abdulaziz Alghannam**

CC **Zoe Asianpour**

FROM Dr Richard Southern, Health and Human Sciences ECDA Chairman

DATE **28 January 2014**

Protocol number: c LMS/PG/UH/00155

Title of study: Evaluation of quality of an oral anti-diabetic (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality.

Your application for ethical approval has been accepted and approved with the following conditions by the ECDA for your school.

Approval Conditions:

Please ensure that the University of Hertfordshire,Health and Human Sciences ECDA is stated on all paperwork as the name of the approving committee;

Please state the protocol approval number above on all paperwork;

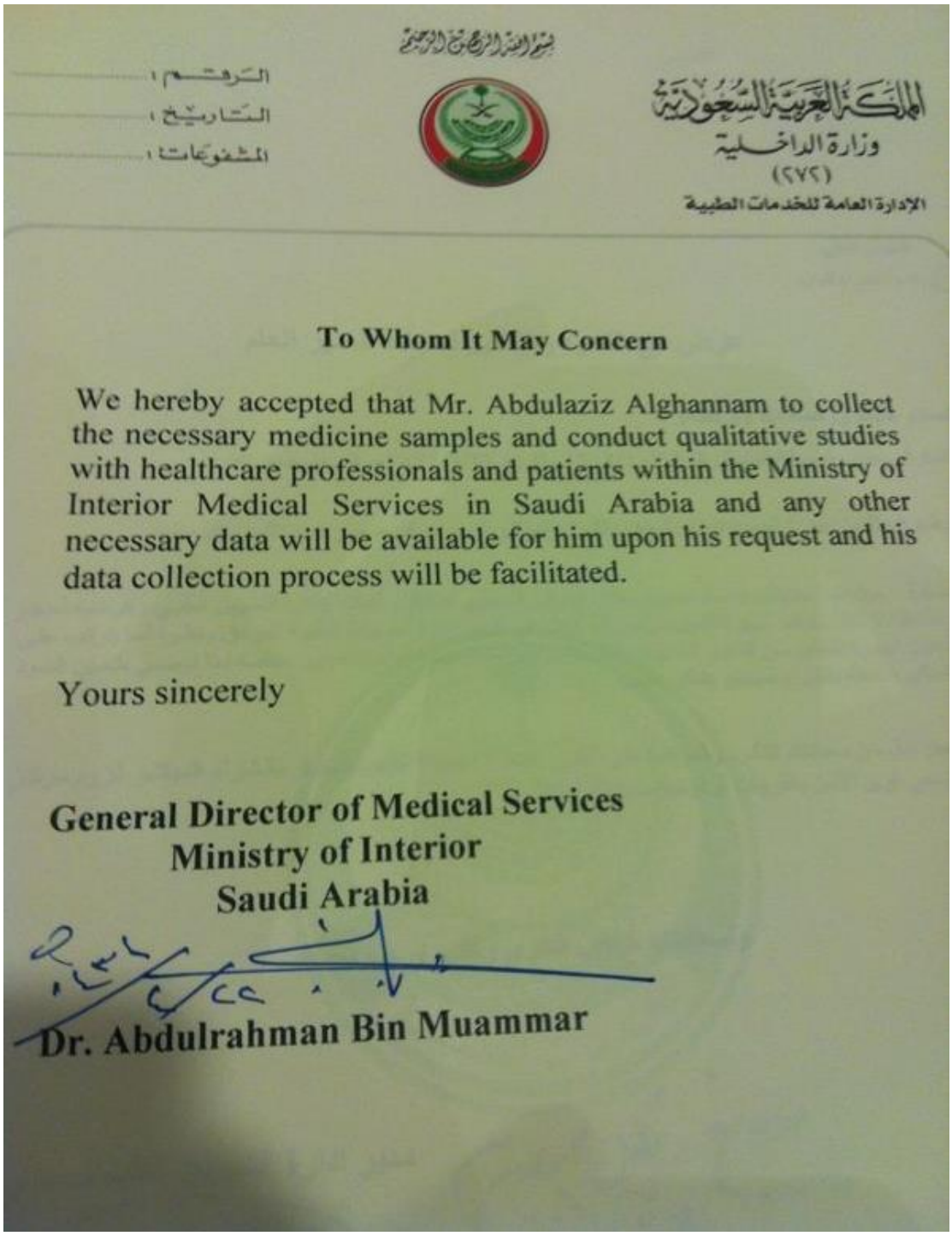
Please ensure that email contact details for the researcher and supervisor are included on all questionnaires;

For interview and questionnaire questions, please consider whether recording participant's marital status is relevant to this study, as it was not noted that you would record this data in your response to Q20 on the EC1. Please remove this question if it is not relevant to your study.

Please confirm that assurance has been sought from Dr Abdulrahman Bin Muammar,General Director of Medical Services, Ministry of Interior,Saudi Arabia that no local ethics approval (or equivalent)is required to approach patients and that the permission letter submitted is all that is required;

Please amend the consent form (EC3) to reflect that it is being used for focus groups/interviews and include consent from participants to be recorded by video/ audio as appropriate;

Appendix 10: MOI-MSD initial approval letter for the study



المملكة العربية السعودية
وزارة الداخلية
(٢٧٢)
الإدارة العامة للخدمات الطبية

الرقم :
التاريخ :
المشفوعات :

To Whom It May Concern

We hereby accepted that Mr. Abdulaziz Alghannam to collect the necessary medicine samples and conduct qualitative studies with healthcare professionals and patients within the Ministry of Interior Medical Services in Saudi Arabia and any other necessary data will be available for him upon his request and his data collection process will be facilitated.

Yours sincerely

General Director of Medical Services
Ministry of Interior
Saudi Arabia

Dr. Abdulrahman Bin Muammar

Appendix 11: MOI-MSD approval letter for conducting interviews in the study

بسم الله الرحمن الرحيم

الرقم: ٣٢/٤/١٢٢٦
التاريخ: ١٤٣٥/٣/١٥
المشفوعات: .....

المملكة العربية السعودية
وزارة الداخلية
(٢٧٢)
الإدارة العامة للخدمات الطبية

To Whom It May Concern:

This is to certify that MR. Abdulaziz Fahad Abdulaziz Alghannam will be conducting a study on Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality at the Ministry of Interior Medical Services Department facilities in Riyadh, Saudi Arabia. This is part of his PhD studies at the university of Hertfordshire, Hatfield, UK. The study is scheduled to start on February 15th 2014 until May 15th 2014.

He has been given this letter upon his request to submit to the Saudi Cultural Bureau in London, UK.

General Director of Medical Services Department
Ministry of Interior

Nasser Bin Abdullah Al-Muhainy

Appendix 12: Participant information sheet for the focus group phase of the study

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

Title of Research

Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality

Introduction

You are being invited to take part in a research study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

The purpose of this study is explore perceptions about medicines quality and related medicine quality issues from the perspective of the Ministry of Interior Medical Services Department (MOI MSD) healthcare professionals and patients. The research may also involve perceptions from other industries such as the Ministry of Health employees in Saudi Arabia particularly in the question design phase at the beginning of the project.

Do I have to take part?

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason.

What will happen to me if I take part?

If you decide to take part in this study, you will be involved in it for approximately three hours on one specified date. It is likely that the discussion would be video recorded for data analysis purposes where possible.

The first thing to happen will be that the researcher will send you an invitation letter to participate in the study along with suggested dates for the discussion via electronic mail. Participants will then send a reply agreeing to participate if they wish along with their preferred times and dates. The researcher will then decide the most appropriate time, date and location for meeting with the participants and send an electronic mail to them to confirm it. The researcher will also attempt to contact all participants two days

prior to the discussion date as a reminder. On the specified date for the study, the researcher and his team will be waiting for participants to arrive at the study location and consent forms and demographic data will be collected before the start of the focus group discussion.

What are the possible disadvantages, risks or side effects of taking part?

We anticipate no major disadvantages, risks or side effects to your participation. We are interested in your perception regarding the subject of medicine quality. We aim not to disturb your daily life and every effort will be made to make your participation as convenient to you as possible.

What are the possible benefits of taking part?

Your involvement in this study is of paramount importance. You will be part of a study that will explore different perceptions about medicine quality issues from the perspective of both healthcare professionals and patients in Saudi Arabia. Outcomes from this study could result in highlighting new areas of concern about perceptions of medicine quality and could also lead to improvement on current policy/practice to better ensure and protect the quality of your medicines. Additionally, this study could be fundamental to other similar studies about medicine quality issues in Saudi Arabia or internationally.

How will my taking part in this study be kept confidential?

Participation in this study will be kept confidential and your involvement anonymous at all times. No names will be published in any report and all hard copy personal information will be kept with the researcher only at all times. Electronic material will be password protected and access to this information will be restricted to the research team only. The collected material will be available for a short period of time (2 years approximately) and then it will be destroyed.

What will happen to the results of the research study?

The results of this study will be used in academic publications by the researcher. However, no individuals will be named or identified at any point in time.

Who has reviewed this study?

The Ethics Committee at the University of Hertfordshire in the United Kingdom has reviewed this research study.

Who can I contact if I have any questions?

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

Abdulaziz Alghannam
PhD student at the University of Hertfordshire, UK
E-mail: Pharmafg@gmail.com
Telephone in UK: 00447732142882. Telephone in Saudi: 0556560655

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

Appendix 13: Participant information sheet for the questionnaire phase of the study

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET (Questionnaire)

Title of Research

Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality

Introduction

You are being invited to take part in a questionnaire study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

The overall purpose of this project is to explore perceptions about medicines quality and related medicine quality issues from the perspective of the Ministry of Interior Medical Services Department (MOI MSD) healthcare professionals and patients. In this study, it is essential to broadly explore attitudes and behaviour regarding medicine quality from the perspective of pharmacists and physicians working in MOI MSD facilities in Saudi Arabia.

Do I have to take part?

It is completely up to you whether or not you decide to take part in this study. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason.

What will happen to me if I take part?

If you decide to take part in this study, you will be involved in it for no longer than 15 minutes and completing the questionnaire will be required only once at a time and date of your convenience.

The first thing to happen will be that the researcher will send you an e-mail invitation letter to participate in a self-completed questionnaire. You will be sent a web link to directly complete the questionnaire online. Alternatively, a Word document file of the

questionnaire will also be available attached to the invitation letter should you prefer not to enter the web link. Please remember to send back the completed questionnaire to the researcher if you have chosen to complete it on the Word document. You are only asked to complete one form of the questionnaire either through the web link or the Word file, please do not complete both forms of the questionnaire, as they are exactly the same. Please note the date for closing the questionnaire survey specified in the invitation letter as no responses can be recorded following this date.

What are the possible disadvantages, risks or side effects of taking part?

We anticipate no major disadvantages, risks or side effects to your participation. We are interested in your perception regarding the subject of medicine quality. We aim not to disturb your daily life and every effort will be made to make your participation as convenient to you as possible.

What are the possible benefits of taking part?

Your involvement in this study is of paramount importance. You will be part of a study that will explore different perceptions about medicine quality issues from the perspective of both healthcare professionals and patients in Saudi Arabia. Outcomes from this study could result in highlighting new areas of concern about perceptions of medicine quality and could also lead to improvement on current policy/practice to better ensure and protect the quality of your medicines. Additionally, this study could be fundamental to other similar studies about medicine quality issues in Saudi Arabia or internationally.

How will my taking part in this study be kept confidential?

Participation in this study will be kept confidential and your involvement anonymous at all times. You will not be asked for your name in the questionnaire and all hard copy personal information will be kept with the researcher only at all times. Electronic material will be password protected and access to this information will be restricted to the research team only. The collected material will be available for a short period of time (2 years approximately) and then it will be destroyed.

What will happen to the results of the research study?

The results of this study will be used in academic publications by the researcher.

Who has reviewed this study?

The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study.
Protocol number: c LMS/PG/UH/00155

Who can I contact if I have any questions?

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

Abdulaziz Alghannam
PhD student at the University of Hertfordshire, UK
E-mail: Pharmafg@gmail.com
Telephone in UK: 00447732142882
Telephone in Saudi: 0556560655

Alternatively, you can contact the principle supervisor of the project as follows:

Dr. Zoe Aslanpour
Head of Pharmacy and Public Health Practice
University of Hertfordshire
Hatfield
AL10 9AB
Tel - 01707 284563
Email - Z.Aslanpour@herts.ac.uk

Acknowledgment:

We recognise that this study may raise fear of medicines with lower quality. If you have such concerns please feel free to share them with the researcher using one of his contact details mentioned above. Alternatively, you can also share these concerns with one of your trusted colleagues within MOI MSD clinics who will provide you with the necessary support that you may require.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

Appendix 14: Participant information sheet for the interview phase of the study

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET (Interview)

Title of Research

Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality

Introduction

You are being invited to take part in an interview study. Before you decide whether to do so, it is important that you understand the research that is being done and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?

The overall purpose of this project is to explore perceptions about medicines quality and related medicine quality issues from the perspective of the Ministry of Interior Medical Services Department (MOI MSD) healthcare professionals and patients. In this study, it is essential to obtain in-depth understanding of attitudes and behaviour regarding medicine quality from the perspective of commissioners and patients in MOI MSD facilities in Saudi Arabia.

Do I have to take part?

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason.

What will happen to me if I take part?

If you decide to take part in this study, you will be involved in it for no longer than one hour on only one occasion at a time and date of your choice.

The first thing to happen will be that the researcher will approach you personally with this participant information sheet and will answer all your questions if you require further information. An informed consent will then be required for your signature and arrangements will be made with the researcher for your preferred time and location for conducting the interview. The researcher will call you as a reminder two days before

the interview date if you decided not to do it on the same time/date you specified earlier. The interview will be tape-recorded for academic purposes unless you prefer it not to be recorded. In this case, the researcher will be taking notes during the conversation. You will not be identified or named in any following publication of this study at all times. Additionally, the interviews will most likely take place at a private room within MOI MSD facilities in order to maintain your confidentiality and no one besides the researcher and yourself will be present unless you specifically ask for the attendance of a particular person.

What are the possible disadvantages, risks or side effects of taking part?

We anticipate no major disadvantages, risks or side effects to your participation. We are interested in your perception regarding the subject of medicine quality. We aim not to disturb your daily life and every effort will be made to make your participation as convenient to you as possible.

What are the possible benefits of taking part?

Your involvement in this study is of paramount importance. You will be part of a study that will explore different perceptions about medicine quality issues from the perspective of both healthcare professionals and patients in Saudi Arabia. Outcomes from this study could result in highlighting new areas of concern about perceptions of medicine quality and could also lead to improvement on current policy/practice to better ensure and protect the quality of your medicines. Additionally, this study could be fundamental to other similar studies about medicine quality issues in Saudi Arabia or internationally.

How will my taking part in this study be kept confidential?

Participation in this study will be kept confidential at all times. No names will be published in any report and all hard copy personal information will be kept with the researcher only at all times. Electronic material will be password protected and access to this information will be restricted to the research team only. The collected material will be available for a short period of time (2 years approximately) and then it will be destroyed.

What will happen to the results of the research study?

The results of this study will be used in academic publications by the researcher. However, no individuals will be named or identified at any point in time.

Who has reviewed this study?

The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study.
Protocol number: c LMS/PG/UH/00155
.

Who can I contact if I have any questions?

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

Abdulaziz Alghannam
PhD student at the University of Hertfordshire, UK
E-mail: Pharmafg@gmail.com
Telephone in UK: 00447732142882
Telephone in Saudi: 0556560655

Alternatively, you can contact the principle supervisor of the project as follows:

Dr. Zoe Aslanpour
Head of Pharmacy and Public Health Practice
University of Hertfordshire
Hatfield
AL10 9AB
Tel - 01707 284563
Email - Z.Aslanpour@herts.ac.uk

Acknowledgment:

We recognise that this study may raise fear of medicines with lower quality. If you have such concerns please feel free to share them with the researcher using one of his contact details mentioned above. Alternatively, you can also share these concerns with your physician or one of your trusted colleagues within MOI MSD clinics who will provide you with the necessary support that you may require.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

Appendix 15: Consent form for participants in the focus group phase of the study

CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

…….
of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as mobile phone number or email address]*

…..…… ..
hereby freely agree to take part in the study entitled

Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality

…….

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, and any plans for follow-up studies that might involve further approaches to participants. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed, and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 I have been given information about the risks of my suffering harm or adverse effects. I have been told about the aftercare and support that will be offered to me in the event of this happening, and I have been assured that all such aftercare or support would be provided at no cost to myself.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

5 I have been told what will be done if the study reveals that I have a medical condition which may have existed prior to the study, which I may or may not have been aware of, and which could affect the present or future health of myself or others. If this happens, I will be told about the condition in an appropriate manner and advised on follow-up action I should take. Information about the condition will be passed to my GP, and I may no longer be allowed to take part in the study.

6 I have been told that I may at some time in the future be contacted again in connection with this or another study.

Signature of
participant……Date……..

Signature of (principal) investigator…… Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

Abdulaziz Alghannam

……

Appendix 16: Consent form for participants in the interview phase of the study

University of Hertfordshire

CONSENT FORM FOR STUDIES INVOLVING HUMAN PARTICIPANTS
Interview Phase

I, the undersigned *[please give your name here*, *in BLOCK CAPITALS]*

…….
of *[please give contact details here, sufficient to enable the investigator to get in touch with you, such as mobile phone number or email address]*

…..…… ..
hereby freely agree to take part in the study entitled

Evaluation of glibenclamide quality: analysis and perceptions of stakeholders' about medicine quality in Ministry of Interior clinical settings

…….

1 I confirm that I have been given a Participant Information Sheet (a copy of which is attached to this form) giving particulars of the study, including its aim(s), methods and design, the names and contact details of key people and, as appropriate, the risks and potential benefits, and any plans for follow-up studies that might involve further approaches to participants. I have been given details of my involvement in the study. I have been told that in the event of any significant change to the aim(s) or design of the study I will be informed, and asked to renew my consent to participate in it.

2 I have been assured that I may withdraw from the study at any time without disadvantage or having to give a reason.

3 I have been given information about the risks of my suffering harm or adverse effects. I have been told about the aftercare and support that will be offered to me in the event of this happening, and I have been assured that all such aftercare or support would be provided at no cost to myself.

4 I have been told how information relating to me (data obtained in the course of the study, and data provided by me about myself) will be handled: how it will be kept secure, who will have access to it, and how it will or may be used.

5 I have been told what will be done if the study reveals that I have a medical condition which may have existed prior to the study, which I may or may not have been aware of, and which could affect the present or future health of myself or others. If this happens, I will be told about the condition in an appropriate manner and advised on follow-up action I should take. Information about the condition will be passed to my GP, and I may no longer be allowed to take part in the study.

6 I have been told that I may at some time in the future be contacted again in connection with this or another study.

7 I have been told that this interview will be audio taped and I agreed to that.

Signature of participant……Date……..

Signature of (principal) investigator…… Date……

Name of (principal) investigator *[in BLOCK CAPITALS please]*

Abdulaziz Alghannam

……...

Appendix 17: Focus group schedule

Collect demographics and participants consent forms

Moderator introduction

Gratitude then explain research aim/objectives using slide presentation (2 minutes)

Hello everyone. My name is Abdulaziz Alghannam and I am PhD student in Pharmacy here at the university of Hertfordshire. I'd like to start off by thanking each of you for taking time to come today. We'll be here for about two hours. The reason we're here today is to get your opinions about issues related to medicines with quality problems.

I'm going to lead our discussion today. I am the facilitator of this meeting and will appreciate your contributions.

I also would like to introduce Dr. Zoe Aslanpour who will be helping me here today.

Ground rules (2 minutes)

To allow our conversation to flow more freely, I'd like to go over some ground rules.

1. Only one person speaks at a time.

2. Please avoid side conversations.

3. Everyone doesn't have to answer every single question, but I'd like to hear from each of you today as the discussion progresses.

4. This is a confidential discussion in that I will not report your names or who said what to anyone. Names of participants will not even be included in the final report about this meeting.

5. We stress confidentiality because we want an open discussion. We want all of you to feel free to comment on each other's remarks without fear that your comments will be repeated later and possible taken out of context.

6. There are no "wrong answers," just different opinions. Say what is true for you, even if you're the only one who feels that way. Don't let the group influence you. But if you do change your mind, just let me know.

Group Discussion

Introduction of participants (2 minutes)

Before we start, it would be good to do a round of introduction. Please tell us:
1- your name 2- your previous pharmacy work experience

General questions (30-45 minutes)

1- What is a good quality medicine in your opinion?
2- What do you think about the quality of medicines in Saudi Arabia? Globally?
3- Have you ever had an experience with a medicine with questionable quality? If yes when and how?
4- In your opinion, what is the relationship between price and medicine quality?
5- In your opinion, what is the relationship between a successful treatment and medicine quality?
6- In your practice, what would you do to ensure supply of good quality medicines to your patients?
7- In your practice, what would you do to protect the quality of medicines for your patients?
8- If you had concerns about the quality of a medicine what would you do?

Specific questions (20-30 minutes)

9- What is a counterfeit medicine in your opinion?
10- What is a substandard medicine in your opinion?
11- What type of medicines are you mostly concerned with in terms of quality and why?
12- What is the possible impact of medicines with lower quality in your opinion?
13- What are possible causes of medicines with lower quality in your opinion?

Suggestion questions (5-10 minutes)

14- What improvements would you suggest to current policies/procedures to ensure that medicines are of high quality in your settings?
15- What advice would you give regarding the topic and to whom?

Moderator presentation (2-3 minutes)

Introduction to the issue and terminology used.
Research aim/objectives and design

Follow up questions (2-3 minutes)

16-What word would you use in Arabic to describe counterfeit medicines?
17-What word would you use in Arabic to describe substandard medicines?

Closing (1 minute)

Thanks for coming today and talking about these issues. I thank you for your time.

We will use the information generated today in developing questionnaires where we will seek stakeholders' perspectives in Saudi. This is part of my PhD study. If you wish to learn about my findings please let me know and I will endeavor to do so.

Appendix 18: Demographic information for focus group participants

Demographic data of participants in focus group

- Gender: ☐ male ☐female

- Marital status: ☐single ☐married ☐divorced ☐widowed

- Age group: ☐ 21-25 ☐26-30 ☐31-35 ☐36-40 ☐over 40

- Working experience: ☐None ☐1-4 years ☐5-10 years ☐more than 10 years

- Type of practice in work experience:

  ☐private ☐public (MOH) ☐public (non-MOH) please specify--------

- Type of setting: ☐hospital ☐primary care clinics ☐community pharmacy

- Location of current practice in Saudi Arabia:

  ☐central region ☐northern region ☐western region ☐eastern region ☐southern region

- Role in current practice:

☐dispensing ☐procurement ☐warehouse ☐management role ☐other please specify-----

Appendix 19: Number of physicians working in MOI-MSD PCC according to 2014 statistical report

جدول يوضح إجمالي الأطباء العاملين بالمراكز الصحية بالمناطق

الجهـــــــة		طبيب عام	باطني	أسنان	أنف وأذن وحنجرة	عيون	نساء وولادة	اطفال	جلدية وتناسلية	نفسية	آخرون	المجموع
المركز الصحي لقوى الأمن بالأحـــساء	سعودي	0	0	0	0	0	0	0	0	0	0	0
	غير سعودي	3	1	3	1	1	1	2	2	0	0	14
المركز الصحي لقوى الأمن بالبـاحـة	سعودي	0	0	1	0	0	0	0	0	0	0	1
	غير سعودي	4	3	1	0	0	1	0	1	0	0	10
المركز الصحي لقوى الأمن بشـــبوك	سعودي	1	0	0	0	0	0	0	0	0	0	1
	غير سعودي	2	2	1	1	1	1	1	1	0	0	10
المركز الصحي لقوى الأمن بجـــدة	سعودي	3	0	4	1	0	0	1	1	0	3	13
	غير سعودي	1	2	0	1	2	3	2	1	2	0	14
المركز الصحي لقوى الأمن بالجـــوف	سعودي	0	0	0	0	0	0	0	0	0	0	0
	غير سعودي	5	2	2	1	1	0	2	1	0	1	15
المركز الصحي لقوى الأمن بجـــازان	سعودي	1	0	0	0	1	0	0	0	0	0	2
	غير سعودي	2	4	2	1	1	0	1	1	0	0	12
المركز الصحي لقوى الأمن بحـائـــل	سعودي	0	0	1	0	0	0	0	0	0	0	1
	غير سعودي	4	2	2	1	1	1	1	1	0	0	13
المركز الصحي لقوى الأمن بالحدود الشمالية	سعودي	0	0	0	0	0	0	0	0	0	0	0
	غير سعودي	5	3	2	1	0	1	1	1	0	0	14
المركز الصحي لقوى الأمن بالـدمـــام	سعودي	1	0	1	0	3	0	0	1	0	9	15
	غير سعودي	4	2	2	1	0	2	0	2	1	0	14
المركز الصحي لقوى الأمن بالطـائـــف	سعودي	1	0	0	0	0	0	1	0	0	0	2
	غير سعودي	4	3	3	1	1	0	1	1	0	0	14
المركز الصحي لقوى الأمن بالعاصمة المقدسة	سعودي	1	0	2	1	0	0	0	0	1	1	6
	غير سعودي	6	3	2	1	1	1	2	2	0	0	18
المركز الصحي لقوى الأمن بعســـير	سعودي	1	0	0	0	0	0	0	0	0	0	1
	غير سعودي	3	3	3	1	1	1	2	1	0	0	15
المركز الصحي لقوى الأمن بالقـريـات	سعودي	0	0	0	0	0	0	0	0	0	0	0
	غير سعودي	1	2	2	0	1	1	1	1	1	0	10
المركز الصحي لقوى الأمن بالقصـــيم	سعودي	1	1	0	0	0	0	0	0	0	0	3
	غير سعودي	4	3	3	1	1	1	2	1	0	0	16
المركز الصحي لقوى الأمن بالمدينة المنورة	سعودي	0	0	0	0	0	0	1	0	0	0	2
	غير سعودي	4	3	3	1	1	2	2	0	0	1	17
المركز الصحي لقوى الأمن بنجـــران	سعودي	0	0	0	0	0	0	0	1	1	0	1
	غير سعودي	0	1	2	0	1	2	1	1	1	0	9
المركز الصحي لقوى الأمن ببيـشـة	سعودي	1	0	0	0	0	0	1	0	0	0	2
	غير سعودي	4	3	3	1	1	1	1	1	0	1	16
المركز الصحي لقوى الأمن بالخـــرج	سعودي	0	0	1	0	0	0	0	0	0	0	1
	غير سعودي	4	1	1	1	1	1	1	1	0	0	11
المجمـــــوع	سعودي	11	1	11	2	4	0	3	3	2	14	51
	غير سعودي	60	43	37	15	16	20	23	20	5	3	242
المجمـــــوع		71	44	48	17	20	20	26	23	7	17	293

Appendix 20: Number of pharmacists working in MOI-MSD PCC according to 2014 statistical report

كما بلغ إجمالي الفنيين العاملين بالمراكز الصحية بالمناطق (460) فنياً يمثلون نسبة (41,4%) من إجمالي العاملين بالمراكز الصحية بالمناطق منهم (192) فنياً سعودياً يمثلون نسبة (41,7%) من إجمالي الفنيين العاملين بالمراكز الصحية بالمناطق ويوضح الجدول التالي إجمالي العاملين الفنيين حسب التخصص والجهة .

الجهـــــــة		صيدلي مرصيدلي	اشعة	مختبر	آخرون	ممرض ممرضة	المجموع
المركز الصحي لقوى الأمن بالأحساء	سعودي	1	0	1	0	0	2
	غير سعودي	2	2	2	0	14	20
المركز الصحي لقوى الأمن بالبـاحـة	سعودي	1	2	3	0	1	7
	غير سعودي	1	1	3	0	8	13
المركز الصحي لقوى الأمن بتـبـوك	سعودي	3	0	1	0	4	8
	غير سعودي	1	1	3	0	12	17
المركز الصحي لقوى الأمن بجـــدة	سعودي	5	4	3	0	3	15
	غير سعودي	1	1	1	0	0	3
المركز الصحي لقوى الأمن بالجـوف	سعودي	2	3	3	0	15	23
	غير سعودي	1	1	0	0	5	7
المركز الصحي لقوى الأمن بجـازان	سعودي	2	0	0	2	0	4
	غير سعودي	1	2	3	0	8	14
المركز الصحي لقوى الأمن بحـائـل	سعودي	1	1	2	0	3	7
	غير سعودي	2	1	1	0	10	14
المركز الصحي لقوى الأمن بالحدود الشمالية	سعودي	3	2	2	0	12	19
	غير سعودي	0	1	1	0	7	9
المركز الصحي لقوى الأمن بالـدمـام	سعودي	1	2	1	3	4	11
	غير سعودي	1	2	4	0	21	28
المركز الصحي لقوى الأمن بالطـائـف	سعودي	1	2	3	1	1	8
	غير سعودي	2	1	3	0	11	17
المركز الصحي لقوى الأمن بالعاصمة المقدسة	سعودي	2	3	4	2	2	13
	غير سعودي	4	2	1	0	12	19
المركز الصحي لقوى الأمن بعســـير	سعودي	7	4	1	1	4	17
	غير سعودي	2	1	3	0	12	18
المركز الصحي لقوى الأمن بالقـريـات	سعودي	2	1	0	1	4	8
	غير سعودي	1	1	3	0	10	15
المركز الصحي لقوى الأمن بالقـصـيم	سعودي	4	2	4	6	2	18
	غير سعودي	2	1	2	0	16	21
المركز الصحي لقوى الأمن بالمدينة المنورة	سعودي	5	3	6	0	3	17
	غير سعودي	0	1	2	0	11	14
المركز الصحي لقوى الأمن بنجـــران	سعودي	1	1	1	0	2	5
	غير سعودي	2	1	3	0	9	15
المركز الصحي لقوى الأمن بهيـشـة	سعودي	1	1	0	1	2	5
	غير سعودي	2	1	1	0	9	13
المركز الصحي لقوى الأمن بالخـرج	سعودي	1	1	0	1	2	5
	غير سعودي	3	1	2	0	5	11
المجمـــــوع	سعودي	43	32	35	18	64	192
	غير سعودي	28	22	38	0	180	268
المجمـــــوع		71	54	73	18	244	460

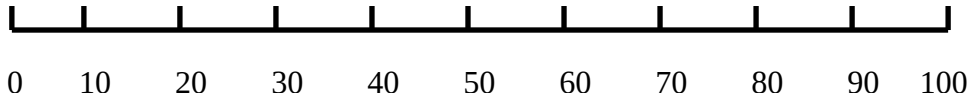
Appendix 21: Physicians' survey questionnaire

Objective one: Establish knowledge and experience about medicine quality

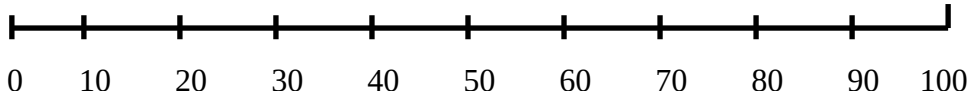
1. In your opinion what is a high quality medicine?

2. In your opinion what is a counterfeit medicine?

3. What in your opinion is the percentage of counterfeit medicines globally?



4. What in your opinion is the percentage of counterfeit medicines in Saudi?



5. Have you ever experienced a medicine with doubtful quality? If yes when and how?

Objective two: Explore perception and behaviour towards medicine quality

6. How would you rate the quality of medicines available in Saudi in general?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

7. How would you rate the quality of medicines available in MOI in general?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

8. How would you rate the quality of medicines you are prescribing now?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

9. When you are prescribing a medicine how important are these attributes to you?
Please rate from 1-10 where 10 represent the highest importance

Your confidence in the medicine's quality of production ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Registration of the medicine in the Saudi FDA ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Lot and expiry date information on the medicine package ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Name of the manufacturing company ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Country of manufacturing ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Patient information leaflet ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Medicine's price ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Your personal experience☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

The experiences of a friend or a family member ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

The availability of the medicine in the market ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

10. In your opinion, do you think that the more expensive medicines are of higher quality than the cheaper alternatives?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

11. In your opinion, how likely would using an expensive medicine be related with better health outcomes?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

12. Would concerns about the quality of a medicine influence your decision to prescribe a medicine?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

13. If you had concerns about the quality of a medicine what would you do? Please select all that apply.

☐ Report to a local doctor
☐ Report to a local pharmacist
☐ Report to the director of pharmacy
☐ Stop prescribing the medicine
☐ Report to the Saudi Food and Drug Authority (SFDA)
☐ Report to the Ministry of Health (MOH)
☐ Do not report it
☐ Other action. Please specify-------

14. How many times a year do you come across medicines with doubtful quality? Please select only one answer.

☐Never

☐Once a year
☐Two to four times a year
☐Five to ten times a year
☐More than ten times a year

15. What medicine therapeutic class are you mostly concerned with in terms of quality? Please select only one answer.

☐None of the therapeutic classes
☐Medicines for treatment of infectious diseases such as antibiotics
☐Medicines for treatment of chronic diseases such as diabetes and cardiovascular diseases
☐Over the counter medicines such as analgesics
☐All therapeutic classes
☐Other therapeutic classes. Please specify--------

16. What type of medicine formulation are you mostly concerned with in terms of quality? Please select only one answer.

☐None of the formulations
☐Injections
☐Tablets or capsules
☐Syrups or suspensions
☐eye/ear drops
☐Creams or ointments
☐Inhalers
☐All formulations
☐Other formulation. Please specify--------

17. What type of medicine issues are you mostly concerned with in your settings? Please select all that apply.

☐No issues of concern
☐Incorrect storage or transportation conditions
☐Packaging is damaged
☐Problems with the appearance of the medicine
☐The medicine contains the wrong or no active ingredient
☐The medicine contains the wrong amount of active ingredient
☐The medicine does not dissolve in appropriate time
☐Medicine is close or past the expiry date
☐Medicine prescribing error
☐Medicine dispensing error
☐Medicine preparation error
☐Limited number of available doses or dosage forms
☐Patients do not accept the available medicines
☐Other issues. Please specify--------

18. How important are these considerations to you before you prescribe a medicine? Please rate 1-10 where 10 is the most important

Clinical effectiveness ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Cost effectiveness to your organisation ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Quality of the medicine ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Affordability to the patient ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Patient safety ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Patient preference ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

19. Have you ever advised any patient to purchase medicines from a community pharmacy? If yes please give reasons.

☐Yes. Reason ----------
☐No

Objective three: Investigate potential improvements to the existing policies and procedure to address the issue of suboptimal medicines in Saudi Arabia in context of global market

20. What changes would you recommend to ensure the high quality of medicines?

Demographics

21. Age: _____

22. Gender: ☐Male ☐Female

23. Location city: _____

24. Occupation: ☐Physician ☐Pharmacist

25. Primary role in organisation: ☐GP ☐Registrar ☐Specialist ☐Consultant

26. Education: ☐BSc ☐MSc ☐PhD

27. Years of experience in MOI MSD: ☐less than one-year ☐1-4 years☐5-9 years ☐10-14 years ☐More than 15 years

Contact details of research team

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

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Telephone in Saudi: 0556560655

Alternatively, you can contact the principle supervisor of the project as follows:

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Hatfield
AL10 9AB
Tel - 01707 284563
Email - Z.Aslanpour@herts.ac.uk

The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study. Protocol number: c LMS/PG/UH/00155

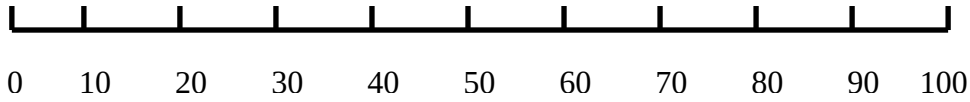
Appendix 22: Pharmacists' survey questionnaire

Objective one: Establish knowledge and experiences about medicine quality

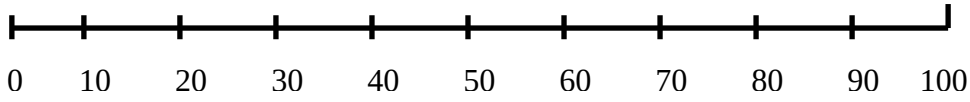
1. In your opinion what is a high quality medicine?

2. In your opinion what is a counterfeit medicine?

3. What in your opinion is the percentage of counterfeit medicines globally?



4. What in your opinion is the percentage of counterfeit medicines in Saudi?



5. Have you ever experienced a medicine with doubtful quality? If yes when and how?

Objective two: Explore perceptions and behaviour towards medicine quality

6. How would you rate the quality of medicines available in Saudi in general?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

7. How would you rate the quality of medicines available in MOI in general?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

8. How would you rate the quality of medicines you are dispensing now?

Please rate 1-10 where 10 is the highest quality ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

9. When you are dispensing a medicine how important are these attributes to you?
Please rate from 1-10 where 10 represent the highest importance

Your confidence in the medicine's quality of production ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Registration of the medicine in the Saudi FDA ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Lot and expiry date information on the medicine package ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Name of the manufacturing company ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Country of manufacturing ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Patient information leaflet ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Medicine's price ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Your personal experience☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

The experiences of a friend or a family member ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

The availability of the medicine in the market ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

10. In your opinion, do you think that the more expensive medicines are of higher quality than the cheaper alternatives?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

11. In your opinion, how likely would using an expensive medicine be related with better health outcomes?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

12. Would concerns about the quality of a medicine influence your decision to dispense a medicine?

Please rate 1-10 where 10 is the most likely ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

13. If you had concerns about the quality of a medicine what would you do? Please select all that apply.

☐ Report to a local doctor
☐ Report to a local pharmacist
☐ Report to the director of pharmacy
☐ Stop dispensing the medicine
☐ Report to the Saudi Food and Drug Authority (SFDA)
☐ Report to the Ministry of Health (MOH)
☐ Do not report it
☐ Other action. Please specify-------

14. How many times a year do you come across medicines with doubtful quality? Please select only one answer.

☐Never

☐Once a year
☐Two to four times a year
☐Five to ten times a year
☐More than ten times a year

15. What medicine therapeutic class are you mostly concerned with in terms of quality? Please select only one answer.

☐None of the therapeutic classes
☐Medicines for treatment of infectious diseases such as antibiotics
☐Medicines for treatment of chronic diseases such as diabetes and cardiovascular
☐Over the counter medicines such as analgesics
☐All therapeutic classes
☐Other therapeutic classes. Please specify--------

16. What type of medicine formulation are you mostly concerned with in terms of quality? Please select only one answer.

☐None of the formulations
☐Injections
☐Tablets or capsules
☐Syrups or suspensions
☐eye/ear drops
☐Creams or ointments
☐Inhalers
☐All formulations
☐Other formulation. Please specify--------

17. What type of medicine issues are you mostly concerned with in your settings? Please select all that apply.

☐No issues of concern
☐Incorrect storage or transportation conditions
☐Packaging is damaged
☐Problems with the appearance of the medicine
☐The medicine contains the wrong or no active ingredient
☐The medicine contains the wrong amount of active ingredient
☐The medicine does not dissolve in appropriate time
☐Medicine is close or past the expiry date
☐Medicine prescribing error
☐Medicine dispensing error
☐Medicine preparation error
☐Limited number of available doses or dosage forms
☐Patients do not accept the available medicines
☐Other issues. Please specify--------

18. How important are these considerations to you before you dispense a medicine? Please rate 1-10 where 10 is the most important

Clinical effectiveness ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Cost effectiveness to your organisation ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Quality of the medicine ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Affordability to the patient ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Patient safety ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Patient preference ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

19. Have you ever advised any patient to purchase medicines from a community pharmacy? If yes please give reasons.

☐Yes. Reason ----------
☐No

Objective three: Investigate potential improvements to the existing policies and procedure to address the issue of suboptimal medicines in Saudi Arabia in context of global market

20. What changes would you recommend to ensure the high quality of medicines?

Demographics

21. Age: _____

22. Gender: ☐Male ☐Female

23. Location city: _____

24. Occupation: ☐Physician ☐Pharmacist

25. Education: ☐BSc ☐MSc ☐PhD

26. Years of experience in MOI MSD: ☐less than one-year ☐1-4 years☐5-9 years ☐10-14 years ☐More than 15 years

Contact details of research team

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

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The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the United Kingdom has reviewed and approved this study. Protocol number: c LMS/PG/UH/00155

Appendix 23: Demographic information sheet for pharmacists and physicians interviews

Demographic information for interview with physician and pharmacists participants

1- Gender: ☐ Male ☐ Female

2- Age: ____

3- City: ____

4- Occupation: ☐ Physician ☐ Pharmacist

5- Education: ☐ BSc ☐ MSc ☐PhD ☐ other please specify _____

6- Experience at MOI-MSD: ☐ Less than one year ☐ 1-4 years ☐ 5-9 years
☐ 10-14 years ☐ 15 years or more

Appendix 24: MOI-MSD medical product quality reporting form

Kingdom of Saudi Arabia
Ministry of Interior
General Administration for Medical Services
P&T Committee

المملكة العربية السعودية
وزارة الداخلية
الإدارة العامة للخدمات الطبية
لجنة الصيدلة والعلاج

MEDICAL PRODUCTS QUALITY REPORTING FORM

Received by:..... Date : / / Serial No.:

A- PRODUCT DETAILS

Type of product: □ Drug □ Vaccine □ Other (specify):.....

Product name (Generic):..... (Brand):.....

Package size:..... Strength:..... Dosage form:.....

Product registration number (if available):..... Batch number:.....

Manufacturer:..... Distributor / Vendor:.....

Manufacturing date:..... Expiry date:.....

Has the manufacturer been informed? □ No □ Yes If so, the date: / /

B- TYPE OF QUALITY PROBLEM

□ Packaging	□ Physical, chemical or microbial changes	□ Questionable stability
□ Suspected counterfeit product	□ Suspected contamination	□ Defective components
□ Product confusion (caused by name, labeling, design or packaging)	□ Labeling Problems (caused by printing errors / omissions)	□ Other:..... .....

□ Therapeutic failure (please provide patient's details):

Patient's name or initials (Optional):..... Date of birth: / /

Age: Weight: Height: Sex: □ M □ F

Health Institute:..... Medical Record No:.....

Description of the problem:.....

.....

.....

C- REPORTER DETAILS

Name: Profession:

Organization: Phone / Mobile: Fax:

E-mail: Date: / / Signature:

**Contact us for any questions or comments E-mail: dpic-moi@hotmail.com Tel: 2466000 Ext: 2131

Appendix 25: Beliefs and views about medicine quality from the stakeholders' views

	Commissioners	Physicians	Pharmacists	Patients
Higher quality medicines provide better health outcomes	Agree (5/6) Do not agree (1/6)	Agree (31/63) Do not agree (12/63) Neutral (17/63)	Agree (37/58) Do not agree (9/58) Neutral (9/58)	Agree (35/53) Do not agree (5/53) No answer (13/53)
Developed countries manufacture superior quality medicines	Agree (5/6)	Agree * (7/8)	Agree * (5/8)	(7/53)
Patients frequently demand brand medicines	Agree (3/6)	Agree * (3/8)	Agree * (2/8)	(2/53)
Medicine quality is different between hospitals in Saudi	0/6	*(2/8)	*(3/8)	(11/53)
Medicine quality differs between manufacturers in Saudi	5/6	*(2/8)	*(2/8)	(12/53)
Medicines do not work similarly for all people	1/6	*(2/8)	*(2/8)	(6/53)
Source of information about medicine quality and issues	Patient's experience (1/6) Personal experience (1/6) Family/friend experience (1/6) Local staff experience (2/6) SFDA letters (3/6)	Patient's reported effect *(3/8) Patient's acceptance *(2/8) Patient's compliance *(1/8) Physician's examination *(3/8) Physician's	Patient's reported effect *(1/8) Patient's acceptance *(3/8) Physician's experience *(1/8) Pharmacist's experience *(1/8) Research studies	Physician's advice (22/53) Pharmacist's advice (2/53) Personal experience (5/53) Family/friend experience (4/53)

		experience *(2/8) Pharmacist's experience *(1/8) Research studies *(4/8) Laboratory analysis *(1/8) Manufacturer reputation *(3/8)	*(1/8) Laboratory analysis *(3/8) Visual analysis *(2/8) Storage conditions *(1/8)	
Therapeutic classes of medicine quality concern Chronic disease medicines Infectious disease medicines All therapeutic classes Other therapeutic classes	 4/6 3/6 1/6 1/6	 9/63 21/63 20/63 7/63	 20/58 15/58 19/58 2/58	Not applicable
Formulations of medicine quality concern Tablets or capsules Injections All formulations Other formulations	 3/6 3/6 2/6 2/6	 22/63 5/63 22/63 9/63	 12/58 15/58 23/58 7/58	Not applicable

Appendix 26: Knowledge about medicine quality

	Commissioners	Physicians	Pharmacists	Patients
Definition of a good quality medicine				
Has good effect	6/6	30/63	22/58	29/53
From a brand company	4/6	1/63	6/58	2/53
Has good appearance/packaging	2/6	0/63	4/58	0/53
Has reasonable price	1/6	4/63	4/58	0/53
Is registered or authorised	1/6	0/63	2/58	0/53
Is accepted by patients	1/6	2/63	0/58	1/53
Has good manufacturing	0/6	1/63	8/58	7/53
Is available	0/6	1/63	2/58	0/53
Is safe	0/6	4/63	4/58	0/53
Has good expiry dates	0/6	2/63	1/58	0/53
Definition of a counterfeit medicine				
Has an effect problem	3/6	26/63	15/58	14/53
Has a manufacturing problem	0/6	1/63	6/58	10/53
Has no API	3/6	1/63	9/58	0/53
Has wrong API	0/6	2/63	3/58	0/53
Has wrong amount of API	4/6	3/63	7/58	0/53
Has an appearance problem	3/6	0/63	3/58	0/53
Is a fake copy of brand medicine	0/6	3/63	7/58	5/53
Is from an unreliable source	0/6	4/63	3/58	3/53
Is a non-registered medicine	0/6	7/63	5/58	2/53
Is a cheaper generic medicine	0/6	1/63	0/58	4/53
Is an expired medicine	0/6	2/63	0/58	5/53
Is a medicine not stored in ideal conditions	0/6	1/63	0/58	2/53

Appendix 27: Challenges to medicine quality in MOI-MSD

	Commissioners	Physicians	Pharmacists	Patients
Tender procurement of medicines is based on price not quality	4/6	*(3/8)	*(4/8)	1/53
Limited or difficulty in reporting medicine quality problems	3/6	*(4/8)	*(3/8)	8/53
Medicine storage conditions in MOI-MSD	1/6	32/63	30/58 *(2/8)	1/53
Medicine transport conditions in MOI-MSD	0/6	32/63 *(1/8)	30/58 *(5/8)	0/53
Expired medicines	0/6	27/63 *(5/8)	29/58 *(2/8)	0/53
Nearly-expired medicines	0/6	*(3/8)	*(4/8)	0/53
Limited budget available to procure medicines	2/6	*(2/8)	*(2/8)	0/53
Outdated medicine formulary	1/6	*(2/8)	*(1/8)	0/53
Inadequate medicine monitoring	0/6	*(1/8)	*(2/8)	3/53
Patients do not accept their medicines	0/6	14/63 *(1/8)	21/58 *(2/8)	0/53
Medicine non-availability	1/6	0/63	0/58	11/53

Appendix 28: Recommendations to improve medicine quality in MOI-MSD

	Commissioners	Physicians	Pharmacists	Patients
Improve medicine monitoring	2/6	9/63	6/58	13/53
Improve medicine analysis	2/6	5/63	4/58	4/53
Improve tender procurement system of medicines	2/6	7/63 *(4/8)	10/58 *(3/8)	4/53
Educational campaigns about medicine and their quality	2/6	3/63 *(5/8)	3/58 *(3/8)	3/53
Improve medicine storage conditions	0/6	8/63	6/58	2/53
Improve medicine transportation conditions	0/6	5/63	3/58	0/53
Ensure medicine expiry dates	0/6	2/63	1/58	2/53
Improve communication among staff and with patients	0/6	2/63 *(3/8)	0/53 *(2/8)	3/53
Update medicine formulary in MOI-MSD	1/6	0/63	1/58	0/53
Conduct research on medicines in MOI-MSD	1/6	0/63	1/58	0/53
Establish a department or a committee for medicine quality	0/6	3/63 *(7/8)	6/58 *(3/8)	0/53

Appendix 29: SurveyMonkey copy of the questionnaire

Information sheet

You are being invited to take part in a questionnaire study in titled Evaluation of quality of an oral anti-diabetic agent (glibenclamide) in Saudi Arabia: analysis and perceptions about medicine quality.The overall purpose of this project is to explore perceptions about medicines quality and related medicine quality issues from the perspective of the Ministry of Interior Medical Services Department (MOI MSD) healthcare professionals and patients.If you decide to take part in this study, you will be involved in it for no longer than 15 minute.Your involvement in this study is of paramount importanceOutcomes from this study could result in highlighting new areas of concern about perceptions of medicine quality and could also lead to improvement on current policy/practice to better ensure and protect the quality of your medicines.You will not be asked for your name in the questionnaire and all hard copy personal information will be kept with the researcher only at all times.The results of this study will be used in academic publications by the researcher.

The Ethics committee at the University of Hertfordshire, Health and Human Sciences ECDA in the UnitedKingdom has reviewed and approved this study.
Protocol number: c LMS/PG/UH/00155

If you would like further information on the research project or would like to discuss any details personally, please get in touch with me by phone or by email:

Abdulaziz Alghannam
PhD student at the University of Hertfordshire, UK
E-mail: Pharmafg@gmail.com
Telephone in UK: 00447732142882
Telephone in Saudi: 0556560655

Alternatively, you can contact the principle supervisor of the project as follows:

Dr. Zoe Aslanpour
Head of Pharmacy and Public Health Practice
University of Hertfordshire
Hatfield
AL10 9AB
Tel - 01707 284563
Email - Z.Aslanpour@herts.ac.uk

Acknowledgment:

We recognise that this study may raise fear of medicines with lower quality. If you have such concerns please feel free to share them with the researcher using one of his contact details mentioned above. Alternatively, you can also share these concerns with one of your trusted colleagues within MOI MSD clinics who will provide you with the necessary support that you may require.

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University Secretary and Registrar.

Thank you very much for reading this information and giving consideration to taking part in this study.

Demographics

***1. Gender**

- Male
- Female

***2. Age**

Age

***3. Location city**

***4. Practice settings**

- Primary care clinic
- Hospital
- Other (please specify)

***5. Primary role in organisation**

- Pharmacy inpatient
- Pharmacy outpatient
- Purchasing
- Warehouse
- Other (please specify)

***6. Education**

- BSc
- MSc
- Phd

Other (please specify)

***7. Years of experience in Ministry of Interior Medical Services Department (MOI MSD)**

- less than one year
- 1 to 4 years
- 5 to 9 years
- 10 to 14 years
- 15 years or more

Introduction questions

***8. In your opinion what is a high quality medicine?**

***9. How would you rate the quality of medicines available in Saudi in general? Please rate from 1 to 10 where 10 is the highest quality**

	1 (worst)	2	3	4	5	6	7	8	9	10 (best)
Medicine quality Saudi	○	○	○	○	○	○	○	○	○	○

***10. How would you rate the quality of medicines available in the Ministry of Interior Medical Services in general? Please rate from1 to 10 where 10 is the highest quality**

	1 (worst)	2	3	4	5	6	7	8	9	10 (best)
Medicine quality MOI	○	○	○	○	○	○	○	○	○	○

***11. How would you rate the quality of medicines you are dispensing now? Please rate from 1 to 10 where 10 is the highest quality**

	1 (worst)	2	3	4	5	6	7	8	9	10 (best)
Quality of medicines dispensed	○	○	○	○	○	○	○	○	○	○

Experience

***12. Have you ever experienced a medicine with doubtful quality? If yes when and how?**

- yes
- no

if yes please specify when and how

***13. How many times a year do you come across medicines with doubtful quality? Please select only one answer.**

- Never
- Once a year
- Two to four times a year
- Five to ten times a year
- More than ten times a year

***14. If you had concerns about the quality of a medicine what would you do? Please select all that apply.**

- Report to a local doctor
- Report to a local pharmacist
- Report to the director of pharmacy
- Stop dispensing the medicine
- Report to the Saudi Food and Drug Authority (SFDA)
- Report to the Ministry of Health (MOH)
- Do not report it
- Other (please specify)

***18. What medicine therapeutic class are you mostly concerned with in terms of quality?**

Please select only one answer.

- None of the therapeutic classes
- Medicines for treatment of infectious diseases such as antibiotics
- Medicines for treatment of chronic diseases such as diabetes and cardiovascular
- Over the counter medicines such as analgesics
- All therapeutic classes
- Other (please specify)

***16. What type of medicine formulation are you mostly concerned with in terms of quality?**

Please select only one answer.

- None of the formulations
- Injections
- Tablets or capsules
- Syrups or suspensions
- eye/ear drops
- Creams or ointments
- Inhalers
- All formulations

Other (please specify)

Variables

***17. When you are dispensing a medicine how important are these attributes to you? Please rate from 1 to 10 where 10 represents the highest importance**

	1 (least important)	2	3	4	5	6	7	8	9	10 (most important)
Your confidence in the medicine's quality of production										
Registration of the medicine in the Saudi FDA										
Lot and expiry date information on the medicine package										
Name of the manufacturing company										
Country of manufacturing										
Patient information leaflet										
Medicine's price										
Your personal experience										
The experiences of a friend or a family member										
The availability of the medicine in the market										
Clinical effectiveness										
Patient safety										
Patient preference										

***18. In your opinion, do you think that the more expensive medicines are of higher quality than the cheaper alternatives? Please rate from 1 to 10 where 10 is the most likely**

	1 (least likely)	2	3	4	5	6	7	8	9	10 (most likely)
Expensive is higher quality										

***19. In your opinion, how likely would using an expensive medicine be related with better health outcomes?Please rate from 1 to 10 where 10 is the most likely**

	1 (least likely)	2	3	4	5	6	7	8	9	10 (most likely)
Expensive equals better health										

***20. Would concerns about the quality of a medicine influence your decision to dispense a medicine? Please rate from 1 to 10 where 10 is the most likely**

	1 (least likely)	2	3	4	5	6	7	8	9	10 (most likely)
quality influences dispensing										

Counterfeit

***21. In your opinion what is a counterfeit medicine?**

***22. What in your opinion is the percentage of counterfeit medicines globally?**

	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
% counterfeit globally	○	○	○	○	○	○	○	○	○	○	○

***23. What in your opinion is the percentage of counterfeit medicines in Saudi?**

	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
% counterfeit Saudi	○	○	○	○	○	○	○	○	○	○	○

Closing

***24. What type of medicine issues are you mostly concerned with in your settings? Please select all that apply.**

- [ ] No issues of concern
- [ ] Incorrect storage or transportation conditions
- [ ] Packaging is damaged
- [ ] Problems with the appearance of the medicine
- [ ] The medicine contains the wrong or no active ingredient
- [ ] The medicine contains the wrong amount of active ingredient
- [ ] The medicine does not dissolve in appropriate time
- [ ] Medicine is close or past the expiry date
- [ ] Medicine prescribing error
- [ ] Medicine dispensing error
- [ ] Medicine preparation error
- [ ] Limited number of available doses or dosage forms
- [ ] Patients do not accept the available medicines
- [ ] Other (please specify)

***25. What changes would you recommend to ensure the high quality of medicines?**