Registration Requirements for Herbal Medicines in Kuwait and Internationally

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Contents

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List of Abbreviations

ADRs	Adverse Drug Reactions
AUS	Assistant Under-Secretary
BfArM	The Federal Institute for Drugs and Medical Devices Germany
CAM	Complementary and Alternative Medicine
CEO	Chief Executive Officer
CPP	Certificate of Pharmaceutical Product
DRA	Drug Regulatory Authority
DRRS	Drug Registration and Release Superintendent
DSHEA	Dietary Supplement Health and Education Act
EBP	Evidence based policymaking
EMA	European Medicines Agency
EMR	Eastern Mediterranean Region
EU	European Union
FSC	Free Sale Certificate
GCC	Gulf Cooperation Council
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HICs	High Income Countries
HIV	Human Immunodeficiency Virus
HM	Herbal Medicine
HMR	Herbal Medicine Registration
IDI	International Development Ireland
ISO	International Organisation for Standardisation
KDFCA	Kuwait Drug and Food Control and Administration
LMICs	Low and Middle-Income Countries
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MOH	Ministry of Health

NDI	New Dietary Ingredient
NHRA	National Health Regulatory Authority
PPC	Pharmaceutical Product Classification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QC	Quality Control
QMS	Quality Management System
SCH	Supreme Council of Health
SFDA	Saudi Food and Drug Authority
SWOT	Strengths, Weaknesses, Opportunities and Threats
THM	Traditional Herbal Medicine
THR	Traditional Herbal Registration
TORC	Theory of Organisational Readiness for Change
UAE	United Arab Emirates
UK	United Kingdom
UREC	Manchester Research Ethics Committee
US	United States
US FDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organisation

Abstract

Background Industrially manufactured herbal medicines (HMs) are historically popular and their consumption continues to increase. As HMs use increases, identification of adverse effects occur more frequently. In some countries' national drug regulatory authorities (DRAs), clear premarketing legislative controls were developed and implemented to ensure the safe use of HMs. In other countries, Kuwait specifically, the premarketing quality, safety and efficacy evaluation of imported HMs is performed with some ambiguity since the DRA does not have a structured classification system in place. This thesis aimed to make recommendations of policy design and implementation of a suitable definition and classification for imported HMs into Kuwait, and explore implementation readiness there.

Methods The policymaking cycle by Anderson was used to frame this programme of research which was conducted in four stages. Stage one and two consisted of documentary analysis and comparisons of HM registration systems in five countries: United Kingdom (UK), Germany, United States (US), United Arab Emirates (UAE) and Bahrain, and a review of published empirical evidence on factors that may facilitate or impede medicine policy implementation. With University ethics and relevant DRAs' approval, stage three and four consisted of thematic analysis of observations and document review of the registration process, and semi-structured interviews with stakeholders in Bahrain as a country which has recently introduced HM regulations. Evaluation of the Bahraini HM registration system, together with findings from stage one allowed policy recommendations for Kuwait, which were followed with further observations, document review and interviews on the Kuwaiti DRA's readiness for implementation, using the Theory of Organisational Readiness for Change.

Results Findings from stage one demonstrated that while there is a diversity in how the five countries define and register HMs, UK, Germany, UAE and Bahrain offer adequate classification and sufficient evaluation procedure based on long standing traditional-use plausible efficacy of HMs. The US, however, offer an unevaluated passage of HMs into the market under the classification of dietary supplements. Findings from stage two revealed that literature on implementation experiences concerning HMs policies in DRAs is lacking and the existing policy implementation research on medicines require a more reliable methodological underpinning. Findings from stage three revealed that the implementation of the classification policy in Bahrain encountered several barriers but ultimately resulted in a more consistent and clearer HM registration process. This allowed recommendations based on the traditional-use classification to be proposed for Kuwait. Findings from stage four revealed that almost all interviewed officials welcomed the proposed recommendations, however the culture of how work is conducted in the authority may impede a successful implementation.

Conclusions Using experiences and insights from stages 1-4, the final policy recommendations consisted of adoption of a universal harmonised HM definition and implementation of the traditional-use registration. An implementation roadmap involving planning for human and technical resources and promoting a professional organisational culture were proposed. Additional research with regards to the evaluation of the HM classification policy would be beneficial to contribute to the currently composed insights.

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The Author

Azhar H. Alostad is a Kuwaiti pharmacist. She achieved her pharmacy degree (MPharm) from the University of Bradford/ UK in 2012 and completed her MSc in Pharmaceutical Services and Medicines Control from the University of Bradford/UK in 2013. The focus of her MSc degree was managing drug supply, drug procurement, drug regulations and licensing, natural products, drug testing and assurance of drug quality. Her MSc thesis aimed at recommending suitable drug donation guidelines for Kuwait and internationally. Soon after obtaining her MSc, she worked as a scientific reviewer in the Pharmaceutical Department at Kuwait Drug and Food Control and Administration (KDFCA) in the Ministry of Health (MOH). Her work as a reviewer covered assessing pharmaceutical applications with New Active Substance (patents) and Existing Active Substance (generics) for the purpose of registration and approval into the Kuwaiti market (through Local Drug Registration), and the Gulf market (through Central Drug Registration). Her work also involved monitoring and setting timelines for product license variations and renewals, advising pharmaceutical manufacturers on regulatory requirements and undertaking pharmaceutical manufacturer regulatory inspections.

In July 2016, she was granted a scholarship from the Kuwaiti MOH to undertake a full-time PhD in Pharmacy. It is hoped that the recommendations of this PhD could be used to inform the herbal medicine registration system in the KDFCA.

Dedication

This thesis is dedicated to my father, Hamoud Alostad, and my mother, Intesar Alqaruni, for their unconditional love, prayers and support. I hope this PhD degree makes you proud.

Acknowledgments

First and foremost, I would like to thank Allah for all the strength and patience he had given me during my PhD and thesis write- up.

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A special thank you to my supervisors, Professor Ellen Schafheutle and Dr Douglas Steinke. I could not have asked for a better supervisory team. Thank you for sharing your incredible knowledge and expertise, and thank you for your endless support, patience, guidance and encouragement throughout this PhD journey. You have helped me develop so many new skills and your eye for detail have enabled me to grow as a researcher and as a person. I will always consider you as my mentors. I would like to acknowledge Professor Darren Ashcroft for his valuable insights and recommendations in the initial design of this thesis. I am also thankful for the support I received from my fellow PhD students and administration staff.

I extend my deepest gratitude to my idol and the former Assistant Under-Secretary of the Kuwaiti Ministry of Health for Medicines and Medical Equipment, Dr Omar Alsayed Omar. Thank you for granting me the opportunity to pursue my PhD, and thank you for your continuous guidance and your confidence and belief in me. I will be forever grateful to you. Special thanks to the former Medicines Laboratory Superintendent at the Kuwaiti Ministry of Health Drug and Food Control and Administration, Ramy Behbahani. Thank you for your continuous support and encouraging me to go over and above. More importantly, thank you for proving that a boss can be a friend as well.

I would like to thank my dad for his words of wisdom in making the most difficult issues so simple and for his words of empowerment and dedication. For setting a great example of hard work paying off and to never give up. I would like to thank my mum for her unending love, support and prayers. I would not be the person I am today if it were not for your continuous guidance. I would like to thank my siblings and extended family and friends for their support and encouragement. A special thank you to my sister Anaam, for caring and for simply listening to my challenges.

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List of Publications and Presentations

Publications

Papers

1. Alostad AH, Steinke DT, Schafheutle EI. Herbal medicine classification: policy recommendations and implementation roadmap. Front. Med. 2019; under review.

2. Alostad AH, Steinke DT, Schafheutle EI. Medicine policy implementation in drug regulatory authorities: a review of the literature. BMC Complem Altern M. 2019; under review.

3. Alostad AH, Steinke DT, Schafheutle EI. A Qualitative Exploration of Bahrain and Kuwait Herbal Medicine Registration Systems: Policy Implementation and Readiness to Change. J Pharm Policy Pract. 2019; 12: 32. Available from: https://doi.org/10.1186/s40545-019-0189-7

4. Alostad AH, Steinke DT, Schafheutle EI. International comparison of five herbal medicine registration systems to inform regulation development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain. Pharmaceut Med. 2018; 32(1), 39-49. Available from: doi: 10.1007/s40290-018-0223-0

5. Alostad AH, Steinke DT, Schafheutle EI. Herbal medicines pre-marketing registration process in the State of Kuwait: An up-to-date overview of the process. J Pharmaceut Res. 2017; 2(2):1-4. Available from: https://pdfs.semanticscholar.org/eb82/c765d9c0154650ecb28aedf0838aa8fb4015.pdf

Abstracts

1. Alostad AH, Steinke DT, Schafheutle EI. Strengths and weaknesses of the herbal medicine registration system in Bahrain. Presented at the International Conference on Plant Science & Natural Products, Medical Plants and Traditional Medicines, Paris, France; 15-16 November 2018. J. Agric. Sci. 2018; 2:38. Available from: DOI: 10.4066/2591-7897-C1-003

2. Alostad AH, Steinke DT, Schafheutle EI. Implementation of a herbal medicine classification system in Bahrain: facilitators and barriers. Presented at the 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences, Glasgow, United Kingdom; 2-6 September 2018. 2018 International Pharmaceutical Federation (FIP) Congress in Glasgow proceedings. Available from: https://www.fip.org/abstracts?page=abstracts&action=generatePdf&item=20725

3. Alostad AH, Steinke DT, Schafheutle EI. International comparison of five herbal medicine registration systems to inform regulation development in Kuwait. Presented at the International Conference on Medical, Biological and Pharmaceutical Sciences, Prague, Czech Republic; 21-22 February 2018. Proceedings of 107th IASTEM International Conference, p.7. Available from: http://www.worldresearchlibrary.org/up_proc/pdf/1404-15226517227.pdf

4. Alostad AH, Steinke DT, Schafheutle EI. Herbal medicines pre-marketing registration process in the State of Kuwait: An up-to-date overview of the process. Presented at the 7th International Conference and Exhibition on Pharmaceutical Regulatory Affairs and IPR, Chicago, USA; 25-27 September 2017. Pharm Regul Aff. 2017; 6(2):69. Available from: DOI: 10.4172/2167-7689-C1-028

Presentations

External

1. Alostad AH, Steinke DT, Schafheutle EI. Kuwait's readiness to implement an herbal medicine classification guideline. Presented at Dubai International Pharmaceutical & Technology Conference & Exhibition (DUPHAT), Dubai, United Arab Emirates; 26-28 February 2019 (poster and oral presentation)

2. Alostad AH, Steinke DT, Schafheutle EI. Strengths and weaknesses of the herbal medicine registration system in Bahrain. Presented at the International Conference on Plant Science & Natural Products, Medical Plants and Traditional Medicines, Paris, France; 15-16 November 2018 (poster and oral presentation)

3. Alostad AH, Steinke DT, Schafheutle EI. Implementation of a herbal medicine classification system in Bahrain: facilitators and barriers. Presented at the 78th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences, Glasgow, United Kingdom; 2-6 September 2018 (poster)

4. Alostad AH, Steinke DT, Schafheutle EI. International comparison of five herbal medicine registration systems to inform regulation development in Kuwait. Presented at the International Conference on Medical, Biological and Pharmaceutical Sciences, Prague, Czech Republic; 21-22 February 2018 (oral presentation)

5. Alostad AH, Steinke DT, Schafheutle EI. Herbal medicines pre-marketing registration process in the State of Kuwait: An up-to-date overview of the process. Presented at the 7th International Conference and Exhibition on Pharmaceutical Regulatory Affairs and IPR, Chicago, USA; 25-27 September 2017 (poster)

Internal

1. Recommending guidelines for the registration of herbal medicines: research highlights. Drug Usage & Pharmacy Practice Group (DUPP) meeting; 7 February 2019 (oral presentation)

2. Implementation of a herbal medicine classification system in Bahrain: Facilitators and barriers and lessons for other countries. Division of Pharmacy and Optometry (DPO) Showcase; 20-21 September 2018 (poster)

3. Recommending guidelines for the registration of herbal medicines in Kuwait: overview and strategy of my PhD. Division of Pharmacy and Optometry (DPO) Showcase; 21-22 September 2017 (oral presentation)

1. Chapter One: Introduction

The purpose of this chapter is to introduce the topic of this programme of research, state the contributors, and provide an outline of this thesis.

1.1 Introduction to the Research

Herbal medicines (HMs) have been used historically for various ailments and their consumption continues to increase. As HMs use increases, adverse effects and herb-drug interactions occur more frequently [1], it therefore becomes imperative that relevant drug regulatory authorities (DRAs) put in place appropriate measures to ensure the safe use of HMs. In some countries' DRAs, HMs are well defined and the HM registration system is established under appropriate existing legislation [2]. In other countries however, Kuwait in particular, important pre-marketing regulatory measures for HM registration are lacking, leading to potential safety issues to consumers [3].

Kuwait has a very limited pharmaceutical manufacturing capacity, therefore, all of its HMs are imported. Because of a lack of a clear definition of what constitutes a HM for registration, and absence of a HM classification procedure that guide the most appropriate assessment for quality, safety and efficacy, when registering, the Kuwaiti DRA implements the classification of the product according to the country of origin. As HMs classifications and regulations differ worldwide [4], this creates inconsistency in the evaluation process of HMs in the Kuwaiti DRA, with potential complications for consumer's safety [3]. The aim of this thesis is therefore to inform the HM registration system in Kuwait using existing evidence and primary insights into countries with established HMs registration systems.

1.2 Contributors

The main author, Miss Alostad, took the major role in the production of all research and resultant papers included in this thesis. She conceptualised and designed all the studies, collected the data, carried out the analysis, drafted and revised the manuscripts, and wrote the thesis. The co-authors of the studies, their qualifications and their contributions are presented below:

Ellen I. Schafheutle, MSc, MRes, PhD, FRPharmS, FFRPS

Professor Schafheutle is Miss Alostad's main supervisor. She conceptualised all studies with Miss Alostad, critically reviewed all manuscripts, and provided constructive feedback.

Douglas T. Steinke, BSc (Pharm), MSc, PhD

Dr Steinke is Miss Alostad's second supervisor. He conceptualised all studies with Miss Alostad, and reviewed all manuscripts.

1.3 Thesis Structure

This section consists of the rationale for submitting the thesis in a journal-based format and outlines the structure of this thesis.

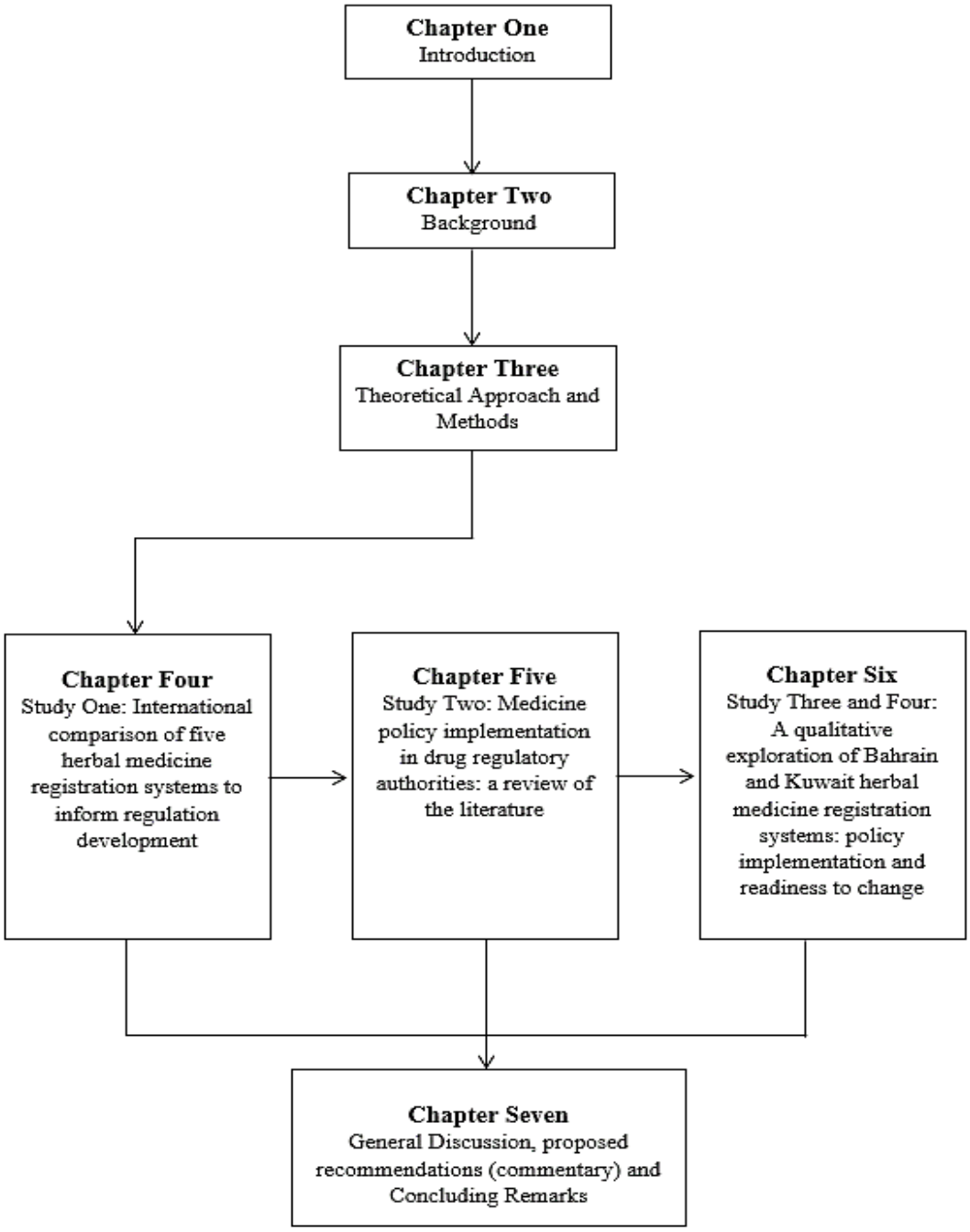
1.3.1 Rationale for submitting in journal format

Aside from the introduction, background, methods and discussion chapters, which are similar for both standard and journal formats, in journal format the chapters presenting different stages of the research are organised as stand-alone papers in a format similar to a manuscript submitted for publication. This format was chosen because the cumulative nature of the research process of this thesis required conducting a series of related studies using different research designs. In other words, findings from each study dictated the design of subsequent studies. The construction of this programme of research, therefore, allowed for individual papers to be produced, which were not only written in the format of journal articles, but three papers have been published and two are under review. This format also assisted the author in acquiring skills and experience writing in journal format.

1.3.2 Outline of the thesis

This thesis aimed to inform the HM registration system in Kuwait. The research process was sequential in nature that addressed one element then moved to address the next one, with each chapter focusing on one or more elements of the thesis. The structure of the thesis is as follows (**Figure 1.1**):

Figure 1.1 Flow chart outlining the organisation of the thesis



This **first chapter** provides an introduction to the programme of research. The **second chapter** then provides the necessary background information about issues and major safety concerns arising from the consumption of HMs and highlights important regulatory challenges associated with HMs. This is followed by the main problem that this programme intended to address, followed by the aim and objectives of the thesis.

The **third chapter** provides a description of the theoretical framework informing this programme of research and provides a rationale for the overall approach taken. This is followed by a description of the data collection and analysis methods employed in each study including any key ethical issues that arose when conducting those studies.

The **fourth**, **fifth** and **sixth chapters** were written in the style of a journal article. The first page of each chapter illustrates if the study has been published, accepted for publication, or is still under review:

The **fourth chapter** consists of the first study of this thesis, which investigated the existing laws of HMs registration in five countries and illustrated a comparison. The paper was published in the Journal of Pharmaceutical Medicine in 2018, presented at the International Conference on Medical, Biological and Pharmaceutical Sciences, Prague in 2018, and the abstract was published in the conference proceedings.

The **fifth chapter** consists of the second study of this thesis, which reviewed published research focusing on factors affecting medicines (including herbals) policy implementation. The paper was submitted for publication in the journal BioMed Central Complementary and Alternative Medicine in 2019 and is currently under review.

The **sixth chapter** consists of the third and fourth studies of this thesis. The third study examined the policy development and implementation process in an established HM registration system (Bahrain) and together with the first study (Chapter Four), harnessed lessons to inform recommendations for Kuwait. These recommendations were used in the fourth study that explored implementation readiness in Kuwait. The two studies were combined to produce one larger paper which was published in the Journal of Pharmaceutical Policy and Practice in 2019. The paper was composed of three key sections, each was presented in a conference. The first section was presented at the International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences, Glasgow in 2018, and the abstract was published in the conference proceedings. The second section was presented at the International Conference on Plant Science and Natural Products, Medical Plants and Traditional Medicines, Paris in 2018, and the abstract was published in the Journal of Agricultural Science and Botany. The third section was presented at Dubai International Pharmaceutical and Technology Conference and Exhibition (DUPHAT) in 2019.

The **seventh chapter** summarises the key findings for each study in this programme of research. Final recommendations of the policy content and implementation roadmap for Kuwait to consider are presented as a commentary paper which was submitted to Frontier in Medicines in 2019 and is currently under review. Strengths and limitation of the research are then discussed followed by the implications of the findings on practice. This chapter also outlines suggestions for future research and describes reflections of the research on the main author, Miss Alostad.

2. Chapter Two: Background

The purpose of this chapter is to provide the rationale for the research which focuses on informing the herbal medicine registration system in Kuwait. Specifically, this chapter will cover the issues and regulatory challenges of herbal medicines, how these have an effect on an importing country with an unsophisticated registration system like Kuwait, and finally identifies the proposed policy that is expected to address the problem. The chapter concludes by stating the ultimate aim and objectives of the thesis.

2.1 Background

The use of plants for the treatment and prevention of various illnesses is historical. With the revolution of science, there has been a significant surge in acceptance and public interest in herbal medicines (HMs) both in developed and developing countries, with these products being available not only in pharmacies, but also in supermarkets and health stores. It is estimated that up to 80% of the world's population (representing four billion people) consume HMs, either for maintaining general wellbeing or as part of their primary source of health care [4]. The annual global drug market is worth about one trillion British pounds, in which approximately 35% of these medicines are from (herbal) origin [5].

The growing demand and interest in HMs has been attributed to several factors, some of which include high costs of most allopathic medicines, and the dissatisfaction with the results from orthodox pharmaceuticals with the belief that HMs might be safer [4, 6]. In spite of the positive perception of patients on the use of HMs and alleged satisfaction with therapeutic outcomes coupled with their disappointment with conventional medicines in terms of effectiveness and/or safety [7, 8], the problem of HMs safety continues to remain a major issue of concern. The general public regard HMs as safe because they are derived from 'natural' origin [6]. However, similar to conventional medicines, HMs contain active ingredients with different therapeutic properties, and therefore are capable of producing a wide range of adverse reactions ranging from nausea, hypersensitivity, seizures, instability of blood pressure,

excessive bleeding and even death [9]. Numerous cases of poisoning have been reported in literature where products were contaminated with dust, pollen, parasites, microbes, pesticides and toxic heavy metals [10-13]. In the Gulf region, the contamination of HMs with toxic substances and the adulteration of HMs with conventional medicines especially in slimming and sexual performance products, were the highest reported HMs incidents [14, 15]. In the United States (US), 20% of reported hospitalisations are related to the consumption of HMs resulting in drug-related hepatotoxicity [16]. In Western Europe, herbal-drug related hepatotoxicity is considered the second most known cause of drug-induced liver disease [16].

The high demand and consumption of HMs, coupled with the increasing cases of poisoning and life-threatening adverse effects is necessitating that national drug regulatory authorities (DRAs) ensure that appropriate regulatory measures are in place to assess the safe use of HMs. Each country's DRA is the competent agency responsible for the regulation of all medicines including HMs. Medicines registration or licensing is one of the DRA's regulatory measures, which ultimately aim to ensure that every industrially manufactured HM on the market meets the appropriate standards of quality, safety and efficacy. This is achieved by conducting product specific pre-marketing assessments to determine whether the product is suitable and safe for registering/marketing. Submission of adequate documentation from the manufacturing company on quality, safety and efficacy of a HM enables the DRA to use information to assess the safety and suitability of the product for the intended use. While the HM registration system in countries such as Austria, France and Germany is well-established under existing laws [2], in other countries, Kuwait in particular, regulatory measures of registering HMs are lacking causing safety issues to consumers [3, 17].

There are various definitions for what is regarded as a HM [18]. For the purpose of this research, a HM is defined as ''herbal preparations that are manufactured industrially in which the active ingredient(s) is/are purely and naturally original plant substance(s), which is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product''. The term "HM" is used throughout the thesis to describe products matching this definition.

2.1.1 Background of HMs in Kuwait

Kuwait is a small emirate of 17,818 sq. km situated at the top of the Arabian Gulf between Saudi Arabia and Iraq (as shown in **Figure 2.1**). The country has a small population of 4.8 million (of which 30 % are Kuwaiti) [19]. Kuwait is wealthy as it has a significant economic position and strategic importance in world affairs, disproportionate to its geographical and population size. The country possesses about 10% of the world's reserves of crude oil. As a result of the exploitation of petroleum resources, Kuwait has a Gross Domestic Product (annual income) of GBP 150 billion [20].

Figure 2.1 Map of Kuwait and surrounding countries [21]

The exact prevalence rate for HMs consumption in Kuwait is unknown as there is scarcity in published studies around this area. However, in a study that was conducted in 2014 on the usage of complementary and alternative medicine (CAM) among medical and pharmacy students in Kuwait, it was found that 55.2% of participants were CAM users with HMs being the most commonly consumed [22]. Because of the

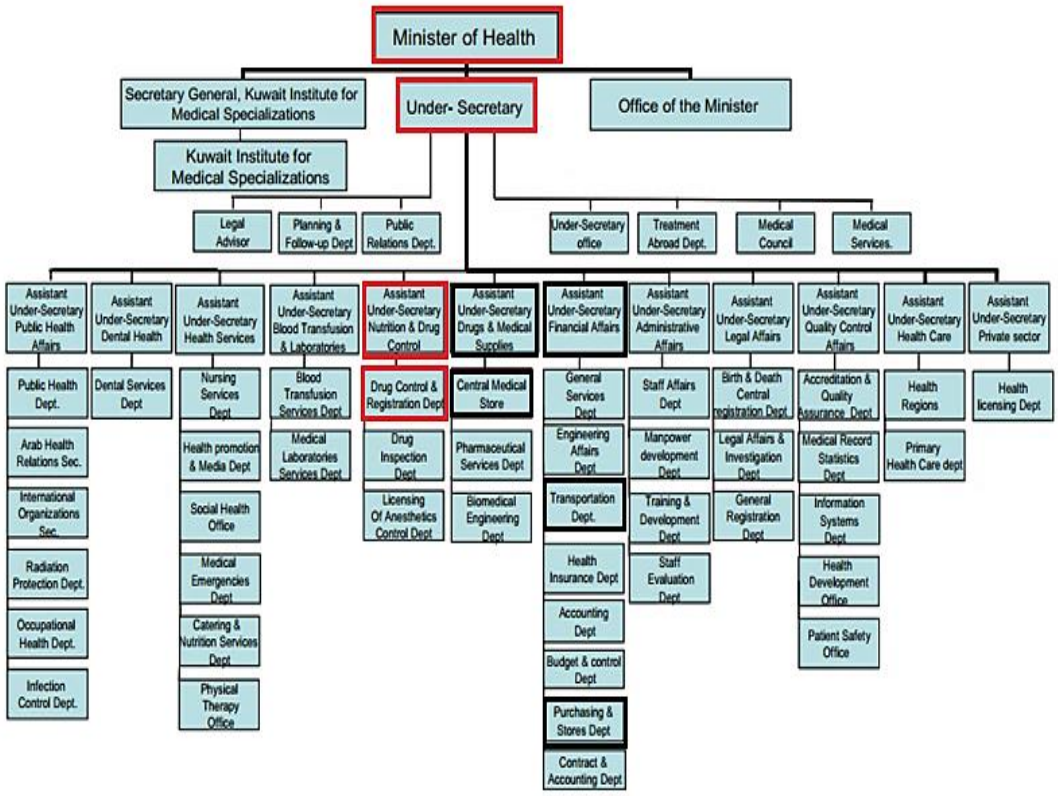
country's small population, the pharmaceutical manufacturing capacity in Kuwait is very limited. Only one pharmaceutical manufacturing company exists in Kuwait; Kuwait Saudi Pharmaceutical Company, which only manufactures generic conventional medicines. Therefore, besides some generic pharmaceutical medicines, all medicines including HMs, dietary/food supplements, medical devices and cosmetics in Kuwait are imported from other countries. In 2016 only, Kuwait spent GBP 819.82 million on importing medicines [23].

Healthcare in Kuwait is mainly delivered in the public health sector and is provided free of charge to Kuwaiti citizens, including all medicines; non-Kuwaitis pay a minimal annual healthcare fee of GBP 130 in addition to the consultation fee GBP 2.64 for every visit to primary care services. Private retail pharmacies and private hospitals are available for those who feel that their needs are inadequately addressed by the governmental facilities or in cases where certain medicines are not provided by the public health sector. Kuwaiti citizens will have to pay for the private facilities and medicines thereafter. Most of CAMs (including many HMs) in Kuwait are provided in private retail pharmacies and sold as over the counter medicines without restriction and can also be found in health stores, which means that the consumer will have to purchase them from their own pockets.

The regulation of HMs in Kuwait with the introduction of specific laws for HMs started in 1989 by the Islamic Medicine Centre. In 1990, the Iraqi invasion of Kuwait caused a seven-month long Iraqi occupation of Kuwait that led to the collapse of the entire healthcare and pharmaceutical regulatory system. In 1991, the war ended, and since then, the regulation of all kind of medicines including herbals are developing. All HMs imported into Kuwait are currently registered and regulated through its official national DRA; Kuwait Drug and Food Control and Administration (KDFCA), a division under the Ministry of Health (MOH) (as shown in the highlighted diagram, **Figure 2.2**). The KDFCA is therefore under the administrative umbrella of the MOH. The MOH holds ultimate responsibility for various aspects of healthcare including regulating the public healthcare sector, monitoring and evaluating the performance of the healthcare sector, providing training to all officials and deciding how healthcare is financed. Although the MOH does not have a role in the regulatory and registration decisions carried out by the KDFCA, developing and implementing policies and regulations of services carried by the KDFCA must be approved by the MOH. The Assistant Under-Secretary (AUS) of nutrition and drug

control serves as a link between policies produced by officials in the KDFCA and the approval of these policies by officials in the MOH.

Figure 2.2 Kuwaiti Ministry of Health organisational structure [24]



2.1.2 Overview of the HM registration system in Kuwait

The registration department in the KDFCA consists of five separate registration units: the pharmaceutical department, herbal department, veterinary department, unclassified department (borderline), cosmetics department and dietary supplement (food supplement) department. The herbal department is responsible for registering HMs as well as herbal teas and coffees. For a HM to be approved into the Kuwaiti market, two main steps must be carried out at the herbal department: agent and company registration, and HM registration.

Because all HMs in Kuwait are imported from other countries- agent and company registration - involves the manufacturing company appointing a local agent to represent the product in Kuwait. This process is a one-off procedure required for the registration of all products. In addition to appointing an agent, the company registration requires the submission of an original and legalised Good Manufacturing

Practice (GMP) certificate and a manufacturing licence from the health authority of the product's country of origin. This is to ensure that the manufacturing company is producing and controlling the product according to high quality standards, which in return minimises the risks involved in any product production that cannot be eliminated through final testing of the product [25]

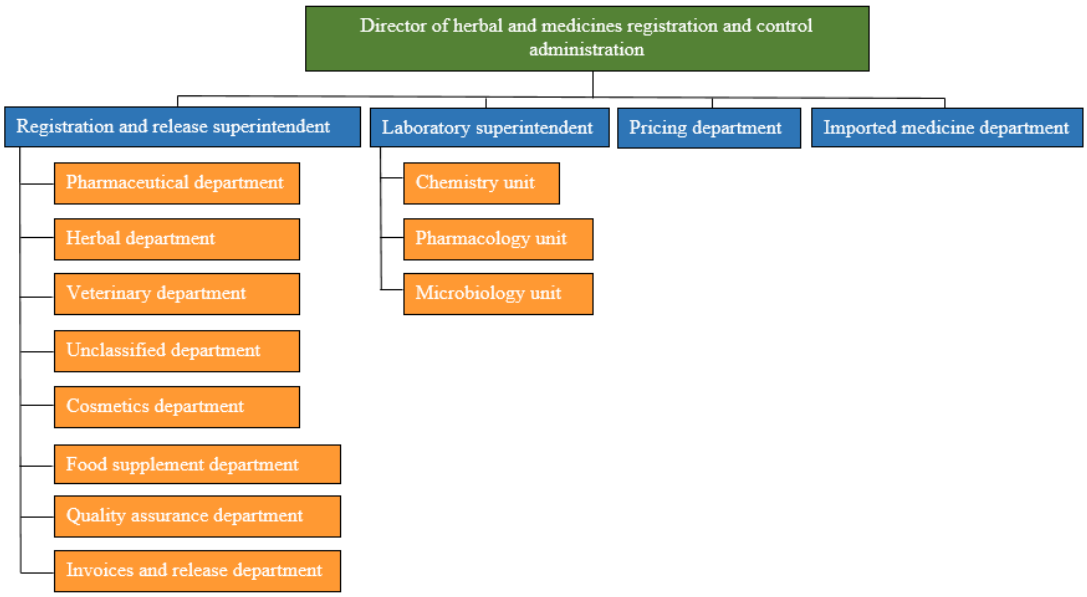
In the second step- HM registration- the agent must submit a sample of the product and a dossier containing documents required for the registration of HMs in accordance with Ministerial Decree 201/9. The dossier must contain an original and legalised Certificate of Pharmaceutical Product (CPP) or Free Sale Certificate (FSC) which establishes the regulatory status of the product in the exporting country, patient information leaflet, artwork of the finished product outer pack and label, original proposed price certificate legalised by the Kuwaiti Embassy in the country of origin, toxicological and clinical studies or evidence of acknowledged scientific references, certificate of analysis of finished product and full stability studies. All products under the herbal department must be analysed in the KDFCA quality control (QC) laboratory prior to their marketing. The QC tests depend on the certificate of analysis of the finished product that the agent provides in the initial submission of the dossier. This certificate is used to compare the specifications on the certificate with the QC analytical results.

2.1.3 The problem

The regulatory status of a HM varies from one country to another [26]. Depending on certain aspects, where a specific HM may be defined as a food or dietary supplement in one country, it may be defined as a herbal or conventional medicine in others. This results in HMs imported into Kuwait being registered under different departments (**Figure 2.3**) in the KDFCA, as the allocation of the product for registration is not based on the nature or characteristics of the product itself, but its regulatory status in the country of origin, which is revealed through the submitted CPP or FSC. Because of the lack of a clear definition of what constitutes a HM and an absence of a clear classification procedure for the registration of imported HMs in the KDFCA, the registration process is uncoordinated. Consequently, some HMs are registered under the unclassified department as dietary supplements or as functional food under the food supplement department, both requiring few and less stringent requirements for

registration. These departments do not require the submission of safety studies and not all products are analysed in the laboratory prior to their marketing.

Figure 2.3 Kuwait Drug and Food Control and Administration registration departments [27]



As a result, some products are marketed with poor quality and safety, resulting in safety issues for the consumers. This is evident in the case of a Kuwaiti young girl who after consuming registered herbal diet pills, experienced a heart attack and severe liver failure resulting in her death [3]. It has therefore became essential to establish a clear definition and classification of HMs in the KDFCA structure, to allow a standardised approach for evaluating imported HMs into Kuwait.

2.1.4 Approach to solving the problem

According to Ratanawijitrasan and Wondemagegnehu [28], in order for a DRA to function effectively, it must function within an administrative environment in the presence of policies that enable a consistent and authoritative process for regulating medicines. Anderson [29] defines policy as a "relatively stable, binding, purposive course of action followed by an actor or set of actors in dealing with a problem or matter of concern", and he classifies it as either substantive or procedural. Substantive policies involve what an organisation is going to do, such as paying welfare benefits or prohibiting the retail sale of liquor. Procedural policies, in contrast, relate to how

something is going to be done, and identifies the actors who are going to take action [29]. So defined, procedural policies include determining the matters over which who have jurisdiction, and specifying the processes and techniques that implementers can use in carrying out their processes. Reforming a policy for the HM registration system in Kuwait requires introducing a suitable classification procedure to carry out the analysis and assessment of HMs, and therefore, requiring a procedural policy.

Efforts in reforming the HM registration system in Kuwait requires rigorous and systematic research, using high quality, valid and reliable evidence [30, 31]. Evidence-based policymaking (EBP) produces well informed decisions about policies and projects by exploring other countries' approaches of the policy in question, ensuring that the decisions are supported and resourced with the best available research [32-34]. Therefore, in efforts for informing the HM registration system in Kuwait, it will be essential to explore other DRAs' approaches to HM definition and classification, in more established systems. Nevertheless, a policy includes not only the decision to adopt a law but also the subsequent decisions that are intended to enforce or implement it [29, 35]. Similarly to using evidence to inform the content of the policy, analysis and evidence on policy implementation experiences in different countries can help understand factors that can have an effect on the success or failure of the policy [36, 37]. Therefore, for the purpose of planning a successful implementation of the policy in the Kuwaiti DRA, it will be essential to perform an analysis on the implementation process of the policy in question (HM definition and classification) in an established system, and explore its strengths and weaknesses. This will improve policy development by reducing uncertainty, increasing logical clarity, providing reliable facts and knowledge and ensuring that the decisions are supported and resourced with the best available evidence and research [38].

However, if the proposed policy decision is to be implemented in Kuwait, some change will need to occur. Lehman, Greener and Simpson stated that change for the sake of change does not necessarily produce a successful conclusion, and implementing systems that are not appropriate with the culture of the organisation may lead to undesirable effects [39]. Therefore, being "ready" for this change in the Kuwaiti DRA is important for successful implementation. Weiner [36] defines readiness as "a state of being both psychologically and behaviourally prepared to take action". Smith [40] argued that there is a high risk of failure if individual or organisational readiness for change is poor. In line with Weiner and Smith, people are

the foundation of change, and it is they who will either welcome or resist it. People react against change for a wide range of reasons, including fear of the unknown, lack of information, threat to status, there being no perceived benefits, fear of failure, low trust in the organisation, strong peer groups norms and being bound by custom [41]. In other words, to succeed in implementing the HM classification policy in the Kuwaiti DRA, staff must be ready for such change. The literature indicates that the best approach is a comprehensive examination of an organisation's readiness for overall change before any attempt to implement such change is made; such an investigation can reveal factors about the potential success of the intended policy, followed by recommendations to increase the readiness should it be found to be defective [36, 42-44].

2.2 Research Aim and Objectives

The aim of this research was to make recommendations for the design and implementation of a definition and classification policy, suitable for initial registration of imported, manufactured HMs into Kuwait. Following the above approach in reforming a policy, the objectives of the thesis are as followed:

1) To compare existing HMs' definition and classification laws in select country DRAs with established HMs systems.
2) To review research evidence on factors that may impede or facilitate policy implementation, particularly with regards to (herbal) medicines regulations.
3) To thoroughly explore the development and implementation process of a HM classification policy in an established system that only imports HMs, including an investigation of the system's strengths and weaknesses.
4) To formulate recommendations of a suitable HM definition and classification policy for Kuwait informed by the findings from objectives 1 to 3.
5) To identify shortcomings of the Kuwaiti DRA system for the registration of imported HMs, and explore the readiness of the Kuwaiti DRA towards implementing the proposed recommendations from objectives 1 and 3.
6) To formulate final recommendations on the policy content and provide an implementation plan for the Kuwaiti DRA from objectives 1 to 5.

3. Chapter Three: Research Philosophy, Theoretical Approach and Methods

The purpose of this chapter is to provide a description of the research philosophy and an overview of the different theoretical approaches to policymaking. Description of the chosen theoretical process, and the theoretical underpinning for the overall approach taken in this thesis is then presented to show where the thesis objectives are placed within that process, followed by a description and rationale of the methods employed in each study including any key ethical issues that arose when conducting those studies.

3.1 Research philosophy

Understanding research philosophy is vital. It reflects on how researchers decide to conduct the research and influence the way they reason about the development of knowledge [45]. The research philosophy also clarifies the research design and its methods for collecting and interpreting the data required to address the research objectives [46]. Different methodologies can be used for a given ontological or epistemological approach. Ontology studies the nature of existence in terms of whether the social world is perceived from an objective or subjective nature. While epistemology- which reflects the nature of this thesis- is the study of knowledge, and it covers three philosophical paradigms, namely, a) positivist, b) critical and c) interpretivist, as these approaches have been used in previous policymaking and organisational research [47-51]. The three paradigms underpin different philosophical assumptions about how to achieve knowledge.

Positivist paradigm aims to enable the prediction and control of a phenomenon, whether physical or emotional by highlighting the objective measures of facts quantitatively [52]. Unlike the positivist approach, the interpretive approach is associated with qualitative measures in order to capture the processes of social certainty [53, 54], and has four characteristics; researcher reflexivity, multiple interpretations, multiple subjective realities and dynamic social understanding of people in their natural settings [55- 57]. The critical and interpretive paradigms are

similar where both approaches contradict the positivist paradigm by building on social reality, which is created by people. But unlike the interpretive paradigm, the critical paradigm does not only emphasise subjectivity, but also encourages objective characteristics that tend to control experiences and perceptions, such as in political, cultural and economic societies or organisations [55].

3.1.1 Paradigm choice and rationale for the chosen research method

Each of the above philosophical approaches has their own set of philosophical principles and own suitable way to perform research [54]. The appropriate choice of a research approach will therefore dictate the choice of method and hence how it addresses the research aim and context [55]. Quantitative and qualitative methods are different in the way they are designed and carried out. According to Myers [56], quantitative research was designed to study natural science using surveys, numerical methods and laboratory experiments. Conversely, qualitative research was designed to investigate studies that are applicable to social sciences, such as investigating a social phenomenon using interviews, observations and documents.

From the above mentioned research philosophies in Section 3.1, a connection can be made between the quantitative research and the positivist paradigm and between the qualitative research and the interpretive paradigm. In order to address the aim of this research, it would require an exploration of other countries' HMs laws and insights into how these laws were developed and implemented, and examine readiness to implementation in the Kuwaiti DRA's organisation. As positivism is generally biased towards deductive, quantified method [58]. In this study, this approach would not allow the researcher to fully capture the richness of the policy processes strengths and weaknesses, and perceptions and readiness for change in relation to HMs policies, as data generated from quantitative methods cannot always completely explain why outcomes occur [58]. As a result, the understanding of processes in a policy may be inconsistent or incomplete. Therefore, a positivist approach is regarded as unsuitable for this study due to its interpretive element. As for the critical approach, though organisational and cultural issues of the Kuwaiti DRA are uncovered, the research did not intend to criticise or control the political or religious situation in the investigated authorities. This makes the interpretive paradigm the most suitable approach for this study, as this will provide a rich multiple subjective realities of the policymaking processes in an organisational setting.

Below is an overview of the different theoretical approaches to policymaking, followed by the chosen theoretical approach informing the programme of research.

3.2 Theoretical Underpinnings of the Research

One of the purposes of implementation science in different areas of professional practice is to achieve an evidence-based approach using systematic research [59]. Since the aim of this research was to formulate policy design and implementation recommendations for Kuwait, it was important to explore how implementation science and policy analysis came about and the frameworks that would facilitate the generation of such recommendations. Exploration into implementation science revealed that research in early policy reforms was empirically driven and did not pay attention to theoretical underpinnings of policymaking. This issue has been reported by Eccles et al. [60] as "an expensive version of trial-and-error". More recently, implementation science has gained a wider interest to establish the theoretical bases of policy reforms and strategies to facilitate their implementation. Implementation science now applies theories adopted from different disciplines including psychology [61], politics [62] and sociology [63], as well as frameworks, models and theories that were developed from within implementation science [64].

3.2.1 Policymaking models, frameworks and theories

Implementation science is defined as "the scientific study of methods to promote the systematic uptake of research findings into routine practice to improve the quality and effectiveness of services" [65], or in this case policies. Two major aims can be identified for the use of models, frameworks and theories in implementation science: 1) guiding the process of producing and translating research into practice, and 2) understanding what influences implementation outcomes [65]. Although models, frameworks and theories are separate concepts, the terms are sometimes used interchangeably in implementation science [66-68]. For example, systematic reviews [69-71] have not distinguished between models and frameworks because they all involve factors found to have an impact on implementation processes and outcomes. However, what is mostly important is not how the approach is labelled; it is important to recognise that these theories, models and frameworks differ in terms of their assumptions and aims which have implications for their use [65].

Theories in the field of implementation science usually imply a predicative approach (e.g. to what extent do the attitudes and beliefs of employees inside the DRA concerning a HM registration policy predict their adherence to this policy in practice?), and seek to explain causal factors of implementation. Models in implementation science are generally used to define or guide the process of translating research into practice (i.e. implementation practice) rather than to analyse what factors influence implementation outcomes (i.e. implementation research). Frameworks in implementation science have a descriptive purpose by revealing factors believed or found to influence implementation outcomes. There are now numerous theoretical approaches to reform policies in implementation science, and some researchers have encountered difficulties in applying the most appropriate approach [66, 72-75]. Models, frameworks and theories of policymaking in implementation science can be categorised into three groups; process models, determinants frameworks, and implementation theories. To aid understanding, below is an explanation of each concept with examples.

3.2.1.1 Process models

A policy as defined earlier, is "a relatively stable, binding, purposive course of action followed by an actor or set of actors in dealing with a problem or matter of concern" [29]. Policymaking thus typically encompasses a flow and pattern of action that extends over time and includes many decisions. Process models in policymaking [29, 76-79] outline important features that need to be considered in implementation practice and usually suggest a number of steps that should be followed in the process of translating research into practice, starting with the identification of a problem or issue, and ending with a set of activities to solve or deal with it. Therefore, models are generally used to describe and/or guide the process of producing and transferring research into practice. Process models have been described as active by Graham et al. [80] because they " guide or cause change". The terminology in process models is not fully consistent, as some of these models are labelled as frameworks, for example the Knowledge-to-Action Framework [81]. The two most common approaches in process models are the "linear" model and the "heuristic" model.

The linear model tends to take a linear approach in which research is simply transferred from policymakers/researchers to users. This model separates the implementation from the formulation of the policy, and takes a sequential fashion. The

heuristic model offers a more systematic approach by dividing policy stages into a cycle, to aid a better understanding of the process. The stages in this model are not regarded as independent from each other, and each stage impacts on the other stages. This model represents a more realistic and continuous process that can either be sequential or uncoordinated, which allows a workable and flexible approach to the analysis and study of policymaking [29, 82]. This model emphasises important aspects that need to be considered in implementation practice such as factors or determinants that may have an effect on the success or failure of the policy, and whether people comply with the policy after implementation [29]. In addition, various research techniques can be adapted into the stages of this model including determinants frameworks and implementation theories [83].

3.2.1.2 Determinants frameworks

Determinant frameworks in policymaking describes general types (also referred to as domains) of factors that are hypothesised or have been empirically found to influence implementation outcomes. Each type of determinant typically comprises a number of impediments (barriers) and/or enablers (facilitators), which are seen as variables that have an impact on implementation outcomes. Evidence about what effects implementation outcomes is potentially useful for developing and executing implementation strategies that aim to reform policies or practices [65]. The determinants frameworks do not address how change takes place, underscoring that they should not be considered theories. The ways in which determinants frameworks were developed were different. Many frameworks [84-87] were developed by synthesising results from empirical studies of facilitators and barriers for implementation success. Other frameworks were based on existing determinant frameworks in different disciplines (e.g. determinants framework by Anderson [29], frameworks by Gurses et al. [88] and Consolidated Framework for Implementation Research [89]). Numerous frameworks were developed through the investigator's own experiences of implementing new policies/practices. For example, the Understanding User Context Framework [90] and Active Implementation Frameworks [91] were both based on the combination of the investigators' implementation experiences and literature reviews.

The context is an integral part of all determinants frameworks [65]. It is generally understood as the conditions or surroundings in which something occurs.

The role of context however varies from studies that interpret the context in terms of physical environment or location in which the projected change is to be implemented [92-94], to studies that assume that the context is something more active that greatly affects the implementation process and outcomes such as political influences [95-97]. Therefore, although implementation science researchers agree that the context is a crucial aspect for understating implementation, there is no agreement regarding how this concept should be viewed, in what ways the context is manifested and the methods by which contextual influences might be described in research.

3.2.1.3 Implementation theories

There are several theories that have been developed or adopted by implementation science researchers to achieve understanding of certain aspects of implementation [98, 99]. One of these critical aspects is adaptation and readiness for change. Adaptation and readiness for change may refer to the preparation, willingness, and commitment of the organisational members, and their resolve to implement a change by developing the collective ability to achieve an effective change process [36]. Repetto [100] reported that the lack of understanding of ways in which to adapt, and the factors that determine practical readiness are some of the most significant aspects that can lead to failure of a policy or a programme. Therefore, identifying and assessing options for adaptation and knowledge of the extent to which individuals are prepared to adapt is critical [101-103].

Like an individual's willingness to adapt, organisational preparation, and willingness such as legal hindrances, lack of funds for changes and poor coordination among employees responsible for implementing reforms are also critical [44]. Researchers have reported widely that when organisational readiness for change is high, its members likely will initiate the change by exerting greater efforts, and exhibiting more determination and greater cooperation, as well as positive attitudes and behaviour that result in smooth, disciplined, and effective implementation with minimal resistance to change [36, 44]. Such an investigation can be determined through employees' perception toward organisation's flexibility to achieve change, and the extent to which they can actively participate in the process [40]. Adaptation theories such as Implementation Climate [104], Absorptive Capacity [105] and Organisational Readiness [106] allows researchers to prioritise perceived readiness

aspects considered to be most critical to be tackled for informing and facilitating future implementation in the best way found [65].

3.2.2 The chosen theoretical approach informing the programme of research

The discussion so far identified the different theoretical approaches used in implementation science. In this section, the most suitable/applicable approach that would guide this programme of research in achieving its objectives is demonstrated.

Since process models as described in Section 3.2.1.1 are used to guide the process of translating research into practice, it was decided that adopting such an approach would be the most suitable method as it outlines policy-making as stages incorporating a problem-solving process that could facilitate the generation of policy design and implementation recommendations for Kuwait. The key argument in Section 3.2.1.1 that a 'linear model' of policy-making is characterised by objective analysis of options and separation of policy development from implementation, eliminated the 'linear model' from being the chosen approach. The 'linear model' fails to consider the complexities of the implementation process, and the proposed policy and action from this model may not be implementable as it presents an ideal view of implementation practice as a step-wise unchangeable process [107]. Many researchers who used this model reported that the actual process of policymaking is not necessarily sequential, underscoring this model lack of usefulness in policy research [66, 108].

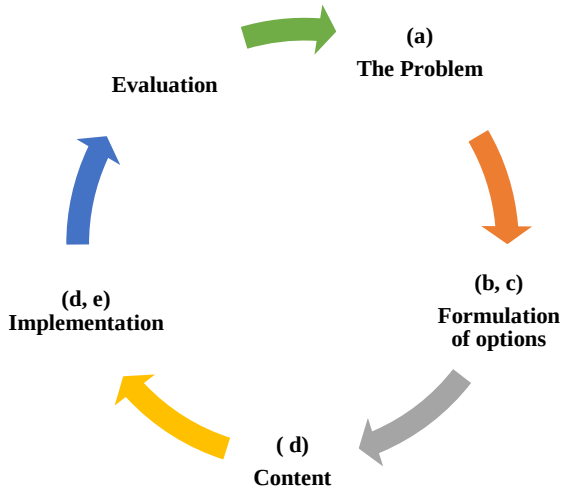
The overarching process of making and implementing policy should indicate that the changes which make up and are part of the policy process occur during both development and implementation, as in the 'heuristic model'. The complex nature of policies and policymaking has led researchers to accept the 'heuristic model' as the most suitable approach to understanding the policy process, making it the most common adapted framework in policy research [109]. This approach has two main aims. First, its primary goal is to explain and analyse existing policy options rather than to formulate a new one, thus saving time and effort. Second, it rigorously searches for the causes and consequences of policy processes by applying social-scientific methodology, requiring that the researcher be rational and empirical.

The term 'policymaking cycle' is considered to define this model, and according to Birkland, this model was studied and developed by various scientists

[109]. Policy scientists define it as a set of interrelated phenomena, processes, work that creates a complete range of actions over a period of time which ultimately lead to the creation of a policy [109]. Although guidance on this model has evolved and its stages have changed, the basic ideas described by all policy scientists remain the same; a problem becomes known, policy-makers analyse it, an appropriate policy is crafted and legitimised, and the policy is implemented and evaluated [109].

The theoretical approach chosen in this research is therefore the 'policymaking cycle/heuristic model'. In his book, 'Public Policymaking', Anderson [29] proposes that the cycle consists of five main steps: identify the problem, formulate options to solve the problem, identify the contents of the selected option, implement the selected option and evaluate the outcome of the implemented option. Other than the specified advantages of this model in Section 3.2.1.1 including the flexibility of applying further determinants frameworks and implementation theories within each of the cycle's steps [83], the policymaking cycle by Anderson was adopted because the objectives of this research are aligned with the four steps of the policymaking (the problem, formulation of options, content and implementation), and were logically and easily situated within the policymaking cycle (**Figure 3.1**) as opposed to other heuristic models that incorporate additional steps which this research did not anticipate to investigate such as policy maintenance, succession or termination [110] or trade off costs-benefits [111].

Figure 3.1 Research objectives placed within the policymaking cycle adopted from Anderson [29]



Having identified the problem (in Section 2.1.3), namely a) the absence of a classification and definition for imported HM registration in the Kuwaiti DRA, the second step (formulation of options) consisted of b) an investigation and comparison of the existing laws of DRA classification and definition of HMs in five countries, and c) review of relevant literature on policy implementation, particularly with regards to HMs regulations. The third and fourth steps (stating the contents of the selected option and implementing it), consisted of d) exploration of the development and implementation process of a HM classification policy in an established system to formulate recommendations, and e) exploration of the readiness of the Kuwaiti DRA towards implementing the proposed recommendations generated from b and d.

Although this research did not perform an in-depth exploration for the final step of the cycle (evaluating the implemented option), general insights on how a policy such as the (HM definition and classification) was evaluated after implementation were generated from the third step (d).

3.3 Choice of Methods and Ethical Considerations

In this research, qualitative methods were the chosen approach to carry out the empirical studies. Qualitative methods, such as interviews and observations, make an important contribution in understanding organisational culture and environment because they can produce detailed information about contexts, processes, and causal pathways [112, 113]. Qualitative methods can capture the depth and complexity of topics, suitable for understating the people's perceptions on events, processes and structures, and can capture unexpected data which may further contribute to the understanding of how processes function [114]. Below is a description of the qualitative methods employed in each study. Methodological issues and ethical considerations in this programme of research are also discussed.

3.3.1 Study One: methods and rationale

In Chapter Two, it was explained that legislative measures regarding HMs have not progressed in a unified structured model [26]. The differences in legislative measures can be a useful aspect triggering a comparison [18]. This will help in understanding other countries' HMs regulatory procedures since Kuwait adopts the regulatory status of herbal products that have been produced, approved and registered elsewhere.

Reviewing other countries' HMs registration procedures reveals how countries register, define and classify HMs and according to what factors, and formulates options for Kuwait to adopt. Therefore, as part of the second step of the policy cycle (formulation of options), the first study of this thesis (Chapter Four) was conducted in 2017, and aimed to compare the similarities and differences between the current HM registration systems of five select countries (UK, Germany, US, United Arab Emirates (UAE) and Bahrain) using document analysis. For details on justifications for the country choice, see Chapter Four, Section 4.2.

Documentary analysis is a form of qualitative analysis that requires official documents to be reviewed and interpreted by the researcher to provide a better understanding of the investigated topic [115]. Documents that are used in document analysis can be in a variety of forms. Since this thesis aimed to inform policy content and implementation for Kuwait, the document type that was used in this study were policy documents. Policy documents are a result of communications, reports, meetings, workshops, submissions, decisions and other activities decided by the main stakeholders in the government [116]. They include regulations, guidelines and legislation information regarding a specific policy.

Documentary analysis has several advantages as opposed to other types of qualitative methods such as interviews or observations. First, it is an efficient method, as it consists of the selection rather than the collection of data. Second, it is a cost-effective method, as the information is publicly available and has already been collected and therefore, it only requires selection and evaluation by the researcher. Third, documents cover many events over a long period and therefore provide with precise and comprehensive details of policies, procedures and references [117]. Fourth, documents are not affected by the research process, which means that it is a nonreactive method; this is different in case of observational methods which the participant is affected and might proceed differently as a result of researchers observing them [115]. Fifth, documents can provide background information, and therefore are helpful in contextualising research within its subject. Sixth, using document analysis in the initial stages of a research can also generate questions that need to be asked or observed, making the use of documents a way to ensure the research is critical and inclusive [115]. However, similar to any other qualitative method, document analysis also has some disadvantages. For instance, a document will not sufficiently provide all the necessary information required to answer the

research question as they may be produced independently from research purposes [115]. Moreover, documents are sometimes difficult to retrieve and might be intentionally kept away from the public. Therefore, it was suggested that to ensure availability, accuracy and validity of documents, only documents that are published by the competent DRA website of each selected country will be taken into account. Official law documents of HMs registration were therefore identified as the five countries official DRAs' websites.

A comparative approach was used in this study, on the basis that countries can learn from one another. There are three major reasons for conducting comparisons between countries [118]. First, comparing country experiences and procedures is a useful approach of developing policies for problem-solving in a particular country. Second, comparing policies can help improve understanding of how organisations operate within their environment, and suggest possibilities for improvement. Third, the interdependence of countries − as reflected by international agreements, unions, collaborations and treaties − is increasing constantly. Therefore, issues that occur in one country can affect other countries more easily and rapidly. Likewise, policies adopted in one country often have important implications for others, and knowledge about what occurs in other countries can help a country prepare to inform its policies.

Data on HM classification, definition and main registration requirements were extracted from each country's official DRA, analysed for similarities and differences across the countries within each specified category, and presented in three comparison tables. The first table compared the HM definition and its registration pathways in each DRA, the second table compared HMs main registration requirements in each DRA, and the third table compared HM classification factors under the different pathways in each DRA. For details on study's inclusion and exclusion criteria, and data collection and analysis processes, see Chapter Four, Section 4.2). Ethical approval for this study was not required, as the study consisted of the extraction of publically available data.

3.3.2 Study Two: methods and rationale

After presenting options of a definition and classification procedure for the registration of HMs from the five-country comparison study there was a need to understand the factors behind policy implementation success or failure. Therefore, as part of the

second step of the policy cycle (formulation of options), the second study of this thesis (Chapter Five) which was updated in 2019, focused on gaining insights into policy implementation by reviewing published research that investigated implementation of medicines policies and regulations including herbals.

Within Anderson's policymaking cycle [29], Anderson explained that the lack of understanding of factors that determine practical execution of the policy is the most significant cause of policy failure. Therefore, he suggested that to guide an effective policy formation, before any implementation attempt is made, it is important to consider factors that can impede (i.e. barriers) or enhance (i.e. facilitators) successful implementation, in order to propose actions to maximise the chance of success and minimise the chance of failure. It is demonstrated that using published research on policy implementation experiences in different countries can help understand factors that enhance or impede policy implementation [50, 51]. Therefore, the aim of this review focused particularly on revealing facilitators and barriers that are relevant to medicines (including HMs) policy implementation in a DRA setting.

The review was performed systematically. The choice for conducting the review systematically was made as systematic reviews are generally regarded as the gold standard of evidence within health research [119]. Reviews that are performed systematically combine the current literature related to a pre-defined research aim into one paper. The paper selection process consisted of four evidence based set of steps for reporting of reviews in a systematic manner; Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA guidelines ensure that reviews that are conducted are of high quality [120]. The steps are used in a transparent way, which means that the study can be easily repeated, and allows for reproduction of the study data at a later date. Key words including words with the same meaning, alternative spelling and plural forms were searched (Appendix 3.1) in three electronic databases. For details on study inclusion and exclusion criteria, and the full search and extraction strategy, and see Chapter Five, Section 5.2. Thematic analysis of included papers was performed. Thematic analysis is a systematic form of qualitative research that records patterns of meaning or 'codes' within data enabling their synthesis to revolve around the same underlying 'theme' [121]. Anderson's determinants of policy implementation are broad and can be used as a logical framework to search for factors that influence how well or how poorly a policy or program has been implemented [29]. Therefore, extraction of facilitators and barriers

was performed using themes from Anderson's four determinants of policy implementation [29].

While quantitative studies follow a rigorous organisation and presentation in how results are presented, qualitative research methodology have been criticised for high levels of subjectivity and low reliability and validity [122]. In response, some qualitative researchers have become increasingly interested in specifying quality criteria for reviews that are specifically suited to the nature of their investigations [123-127]. These sets of criteria are broad and are straightforward and are well-described by Mason [128], and Mays and Pope [129]. Therefore, synthesising implementation experiences from literature also involved a quality assessment of included papers using Mason [128], and Mays and Pope [129] research paper's quality assessment criteria. For details on the data analysis process, see Chapter Five, Section 5.2. Ethical approval for this study was not required as the study was a review of the literature.

3.3.3 Study Three and Four: methods, rationale and ethical approval

Having compared policy options from the first study (first step), and investigated policy implementation facilitators and barriers in the second study (second step), for the third (stating content) and fourth (implementation) steps of the policy cycle, Study Three and Four (Chapter Six) employed a qualitative research design using the case study approach for each step. A case study is an empirical investigation that "investigates a contemporary phenomenon within its real life context when the boundaries between phenomenon and context are not clearly evident" [130]. In case study research, a single or multiple number of cases (individuals or events) are studied by the researcher in great depth [131]. In applying the case study approach, case 1 which was conducted in 2017 focused at gaining insights into a HM registration system of an established DRA (Bahrain) to inform recommendations of a suitable HM classification policy in Kuwait, and case 2 which was conducted in 2018 aimed at exploring the readiness of the Kuwaiti DRA towards implementing these recommendations.

Case 1 performed policy analysis of the PPC policy in the Bahraini DRA using the policy triangle framework by Walt and Gilson [97], to formulate recommendations for Kuwait. In their framework, Walt and Gilson discussed that undertaking policy

analysis is critical for health reforms. They explained that health policy research largely addressed the content of policy, neglecting actors, context and processes. Their policy framework reflects on how all of these four features interact to form policy-making. This framework has been useful in the research of health policy and has been used to analyse many health issues in different countries [132, 133]. Moreover, in order to evaluate the Bahraini's system strengths and weaknesses, SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) was performed in case 1. SWOT analysis is one of the most effective approaches used for analysing strategic management policy of an organisation [134]. Strengths and opportunities are positive factors that support the current registration system and improve its performance while weaknesses and threats impede performance and suggest risks in the current system. Strengths and weaknesses indicate internal conditions while opportunities and threats indicate external conditions [135].

Case 2 focused on identifying the current weaknesses of the system in the absence of a classification and identifying factors that influence the readiness of the Kuwaiti DRA to implement the proposed policy recommendations generated from the second step of the policy cycle (including Study Three). In this study, Wiener's Theory of Organisational Readiness for Change (TORC) was adopted [36]. The theory considers approaching the organisational aspects as possible factors of readiness for implementation. In this study, five contextual factors from TORC were adopted that needed to be investigated to best achieve the aim of the study: policies and procedures, past experiences, organisational resources, organisational culture and organisational structure. Understanding the policies and procedures is important as it may influence how the recommendations can be implemented and detect any governmental concerns that could influence readiness for implementation. Gaining insights on past experiences helps in indicating implementation issues of previously implemented policies. Identification of organisational resources reveals professional and technical issues that could influence readiness for implementation. The organisational culture provides aspects on how individuals behave towards the change that will happen. While the organisational structure factor influences any changes that may affect the infrastructure of the organisation.

Both cases used a mixture of qualitative methods consisting of observations, review of related documents and interviews with a number of key officials in each country's DRA. The senior management of both authorities were contacted to

purposively sample and identify targeted participants in each authority. For details on study participants, see Chapter Six, Section 6.2.1. Identified participants were approached by the main author (Miss Alostad) during the visit in each authority and were given an invitation letter (Appendix 3.2 and 3.3) and information sheet (Appendix 3.4, 3.5, 3.6 and 3.7) about the study.

Interviews and focus groups alone are commonly used qualitative methods in process evaluations [128]. However, evaluation of a specific policy might simply be ignored if it does not investigate how the system functions. Observations are useful in process evaluations to explore the detail of how implemented policies operate [136]. In observations, data collection is direct rather than being reported at a later time point in focus groups or interviews and is unaffected by participant interpretation or the passage of time. This overcomes the problem where employees may not remember or report their activities in an unbiased way for various reasons, such as participants presenting a professional image to researchers or participants making their own descriptions retrospectively. Moreover, observations allow the researcher to record features of everyday life that participants did not feel relevant to disclose in interviews adding to the context of the data. This information deepens and enriches the data, and allows generation of a comprehensive picture of how systems operate. Observations in research consists of two types; participant observation and non-participant observation [137]. Participant observation is when the observer interacts actively with the participants in social activities carried out in a setting. Non-participant observation is when the observer observes participants without actively participating. In this programme of research, the later type of observation was used in case 1 and 2. Field notes were a useful tool in this respect, because they provided not only descriptions of events, but also ongoing interpretations and hints for further focused and selected questions that were later on asked in interviews. Field notes were taken during every stage in the HMs registration process from the initial submission of a product until the approval stage using an observation guide (Appendix 3.8). Field notes recorded were particularly descriptive, since following the stages provided relevant information about the events that occurs while registering a HM.

Document review is a qualitative way of collecting data by reviewing existing documents. Documents may be hard or electronic copy and, may include reports, guidelines, policies and logs. Reviewing existing documents helped understand the classification process and documents required in the registration of HMs in order to

provide a complete picture of the process. Other advantages of this method include being relatively inexpensive, unobtrusive, provides a behind-the-scenes discovery that may not be directly observable and may bring up issues not noted by observations and interviews [138].

Interviews are a useful method for obtaining participants' experiences and knowledge by pursuing in-depth information around the topic under investigation. There are three types of interviews: structured, semi-structured and unstructured. Structured interviews are conducted when the interviewer knows precisely what information is required [139]. Semi-structured interviews are conducted when the interviewer require answers on a particular topic and general discussion while unstructured interviews are used when the interviewer require information to formulate an idea of what areas require future in-depth investigation [139]. According to Oates [55], semi-structured interviews are useful for exploring personal beliefs, views and processes, and allow the participants to speak their thoughts. This allows the participants to express their own opinions more freely in order to formulate a larger or other enquiry. Therefore, both cases used face-to-face semi-structured interviews with participants at their place of work. Signed informed consent (Appendix 3.9 and 3.10) was obtained before starting each interview. It is a requirement that all officials working at both authorities are able to understand, read and comprehend in English to be able to assess and approve international products for registration. However, there were cases that participants were more comfortable in expressing themselves in their first language (Arabic). Therefore, although all interviews were conducted in English, a few also included some Arabic responses. In case 1 the interview guide (Appendix 3.11) was based on a review of the policy science and implementation literature [63, 65, 89, 140, 141]. In case 2 interview questions (Appendix 3.12) were guided by the five contextual factors from TORC [36]. For details on the data collection processes in case 1 and 2, see Chapter Six, Section 6.2.2.

All three sources of data in case 1 and 2 were subjected to thematic framework analysis [142]; a framework commonly used in policy research [143]. It is a deductive frequentative process linked to the aim of the study. Therefore, in both cases, analysis was performed based on the themes in concepts and theories; for case 1 by Walt and Gilson's policy triangle framework [97] and SWOT [135] and for case 2, by themes in Weiner's five contextual factors of TORC [36]. For details on the data analysis processes in case 1 and 2, see Chapter Six, Section 6.2.3.

Ethical approvals for both studies were obtained from the University of Manchester Research Ethics Committee (UREC) (reference number 2017-1086-3939) (Appendix 3.13). A decision to increase the number of participants was made during data collection process in Bahrain and Kuwait, as the author realised that more employees were working directly with the registration of HMs than expected, and therefore were important to be interviewed. Amended UREC approval granted the approvals of these amendments (Appendix 3.14). Permission to conduct research at the Bahraini and Kuwaiti DRA was also obtained from each authority (Appendix 3.15 and 3.16).

3.3.4 Trustworthiness of the research

Reliability in quantitative research refers to findings which are similar, consistent and stable over time, regardless of the number of times the method is repeated [144]. By ensuring that a stable measure remained consistent, findings should be with a high degree of reliability that is repeatable. However, ensuring reliability in qualitative research has been questioned. This is because the term 'reliability' in quantitative research is used for testing repeatability, making it an uncertain, and in some cases, an irrelevant measure in qualitative research [145]. Qualitative researchers recognised that there is a need to establish a qualitative measure that is specific to qualitative research. Therefore, in order to ensure 'reliability' in qualitative research, researchers suggested demonstrating trustworthiness in their studies [146].

According to Merriam [147], "the question of trustworthiness becomes how well a particular study does what it is designed to do". In Study One (five-country comparison study), trustworthiness was confirmed using data that were based on publicly available information obtained through the official website of each country's DRA, which has a responsibility towards the public in providing only valid and up-to-date legal provisions, guidance and procedures about medicines [148]. In Study Two (literature review), trustworthiness was confirmed using data from peer-reviewed papers where included papers were assessed for their validity, quality and originality before publication. Moreover, quality assessment of included papers was also conducted as part of the study's analysis. In Study Three and Four (Bahrain and Kuwait case studies), multiple methods of data collection were used to demonstrate the emerging of findings, and summary of findings were shared with participants. This is consistent with Lincoln and Guba's [123] 'member checks' where interpretation of

empirical data is checked with study participants to ensure validity. Overall, all four studies have undergone (or still are under) peer-review in reputable journals, and internal peer-checking took place to review how the data was collected, as well as the interpretation of data and the plausibility of emerging themes. This was carried out over a number of stages in which the author's PhD supervisors checked the themes and interpretations of the data until all were satisfied.

3.3.5 Ethical considerations

A number of ethical issues were considered during the design and conduct of Study Three and Four. These consisted of self-determination, risk of bias, potential distress, anonymity, confidentiality, and risk assessment and lone working.

Before consenting to take part in the study, potential participants were provided with a participant information sheet that outlined the aims, requirements and duration of the research, what happens to the data collected and if participants change their mind after data has been collected, how confidentiality is maintained, where the research will be conducted and details on what to do if the participant experiences any issues regarding the research (Appendix 3.4, 3.5, 3.6 and 3.7). Potential participants were also given the opportunity to contact the researcher if they had any further enquiries before committing to their involvement. This gave participants the self-determination (freedom of choice) to decide whether they approve or decline to participate [149, 150]. Moreover, to ensure that participants' self-determination was not influenced by the researcher, the researcher addressed the risk of coercion. Whilst the concept of coercion may seem intentional, it commonly occurs unintentionally where participants may feel uncomfortable saying no and, therefore, inclined to take part in a study [151]. To ensure that there was no risk of coercion, potential participants were given up to 48 hours to decide whether they agree to participate or not, and participants who agree to take part were asked to contact the researcher directly.

As the principal researcher was an employee at the investigated authority (Kuwait DRA), this could have influenced the participants and the accounts that they offered during the interviews. One example of this could be participants choosing to be only positive in their opinions of the registration system. However, the principal researcher worked at a separate department (Pharmaceutical Department) which was not one of the investigated departments in the study, and therefore, employees felt more comfortable sharing information about the issues of the different departments.

Moreover, all interviews were conducted in a private room where no one overheard what was being said, and prior to the interviews, participants were assured that their anonymity is guaranteed throughout the entire data collection and analysis process and were assured that no personal information will be recorded. Moreover, in case of a participant feeling distressed/ discomfort during an interview/observation, a distress policy form (Appendix 3.17 and 3.18) was prepared prior to the data collection process. However, the principal researcher did not witness any activity that required using the distress policy form.

It was also important to ensure anonymity and confidentiality by keeping fieldnotes, hard copy data and electronic data anonymised and secure. Data were safeguarded in compliance with the University of Manchester Research Ethical Committee (UREC), the Bahraini DRA and Kuwaiti DRA data management and governance policies. To guarantee anonymity during observations and interviews, each participant was assigned a code and no personal information that is related to participants were recorded. Prior to the interviews, participants were asked not to identify other people or any identifiable information about others during the interview. During observations, if that area was a shared place, a poster (Appendix 3.19 and 3.20) was displayed in the areas where observations took place, so that other officials were aware that research was being conducted. Data collected from interviews by a recording device were transcribed as soon as possible. Electronic data during the data collection process in Bahrain and Kuwait were stored on an encrypted laptop. Once the data collection phase was over, all data collected were stored electronically by the researcher in an encrypted and password protected folder on the University of Manchester computer. Data stored in the laptop were subsequently deleted. Data stored at the University of Manchester were only accessible by the researcher and her supervisors when necessary.

Finally, although it was unlikely that there would be any potential adverse effects, risks of hazards, pain, discomfort, distress or inconvenience to the principal researcher, as the data collection was conducted outside the UK, lone working and risk assessment policy (Appendix 3.21) was followed and reviewed throughout the data collection process. The policy enclosed potential activities that may contain risks, risk rating, measures to control the risk and nomination of a “buddy”. A buddy is a responsible person who knows where the researcher is, when they are expected to

return, and what action to take if the researcher does not return. The buddy exchanged contact details with the supervisor prior to the start of the research.

As this thesis is presented in journal format, the next three chapters will present the programme of work in the format of journal articles for Study One (Chapter Four), Study Two (Chapter Five), and Study Three and Four (Chapter Six). Study Three and Four are written as one long journal article.

4 Chapter Four: Study One

Title	International comparison of five herbal medicine registration systems to inform regulation development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain
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International Comparison of Five Herbal Medicine Registration Systems to Inform Regulation Development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain

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Abstract

Background

Herbal medicine (HM) regulation is less developed than that of allopathic medicines, with some countries lacking specific regulations.

Objective

For the purpose of informing a registration system for HMs in Kuwait, which does not manufacture but imports all HMs, this study compared the similarities and differences between the current HM registration systems of five countries.

Methods

The five countries were selected as major source countries of HM in Kuwait (United Kingdom (UK), Germany and United States of America (USA)) or because of geographical proximity or size and approach (United Arab Emirates (UAE) and Kingdom of Bahrain). Documentary analysis of HM classification systems was performed by reviewing the regulatory and law documentation of these countries' drug regulatory authority websites. Data on HM definition, classification and the main requirements for registration were extracted and analysed for similarities and differences.

Results

There was diversity in the classification of HMs across all five countries including terms used, definitions, type of law, requirements, restrictions and preparation type. The regulatory authorities of the UK, Germany, UAE and Kingdom of Bahrain offer simplified registration for HMs, where plausible efficacy as a result of established traditional use is sufficient. In USA, the concept of traditional use does not exist, instead, the product can be categorised as a dietary supplement where no assessment or evaluation is required prior to marketing.

Conclusions

Owing to the inconsistencies in how drug regulatory authorities define HMs, it will be important to design a clear definition of what constitutes a HM in Kuwait, which is a country that does not produce and register its own products but assesses products registered elsewhere.

Key Points

- To inform the design of a registration system for herbal medicines (HMs) in Kuwait, which does not produce but imports all HMs, the drug regulatory authorities' approaches to HM regulation were compared in five countries.
- There was a lack of consistency in the definition of what constitutes an HM, and how these are assessed, reviewed and regulated.
- Some drug regulatory authorities, USA in particular, do not assess dietary supplements prior to marketing, which has implications for regulatory systems in a country like Kuwait where review currently depends on how a HM is defined and regulated in the source country.

4.1 Introduction

Historically, plants have been used for the treatment and prevention of various illnesses. With the revolution of science, the popularity of herbal medicines (HMs) has widened. It is estimated that 80% of the world's population use HMs in some capacity within their primary healthcare [1]. With the increasing consumer demand, the HM worldwide market is expected to reach US $107 billion by the end of 2017 [2]. As the global use of HMs continues to grow, public health issues related to their safety are also increasingly recognised. The consumption of some HMs has resulted in serious adverse reactions such as hypersensitivity and organ toxicities [1]. HMs have also been found to modify the pharmacokinetics of some drugs [3]. In the Gulf Region, the highest incidences of HMs were attributed to contamination with toxic substances and the adulteration of HMs with conventional medicines especially in slimming and sexual performance products [4].

Given the increasing consumer demand, the market value and potential toxicity, national health authorities have developed laws to ensure the safe use of HMs. In some national markets, such as Germany, France and Austria, HMs are well defined and the HM registration system is well established under existing laws [5]. However, in other markets, such as Kuwait, adequate regulatory measures for HM registration are lacking, leading to safety concerns [6].

For the purpose of this article, HMs are defined as "Herbal preparations that are manufactured industrially in which the active ingredient(s) is/are purely and

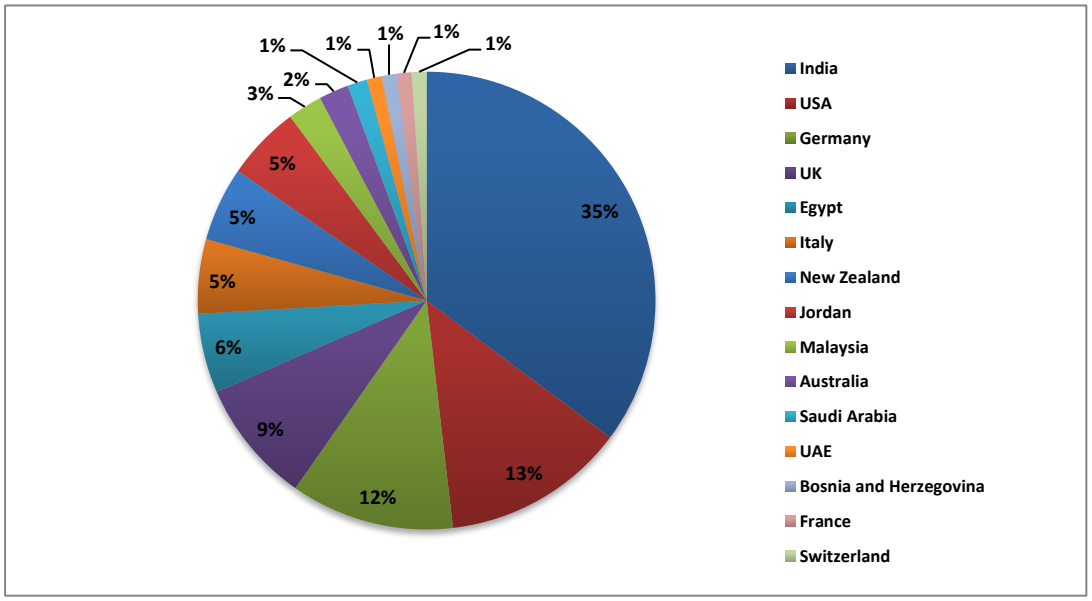
naturally original plant substance(s), which is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product".

4.1.1 Kuwait: a country without a herbal medicine definition and classification system

Kuwait is a small wealthy emirate located at the top of the Arabian Gulf between Iraq and Saudi Arabia. The pharmaceutical manufacturing environment in Kuwait is not very competitive because of the country's small population of 4.4 million (with 30.5% being Kuwaiti) [7]. As a result, all HMs in Kuwait are imported from other countries and registered through the Kuwait Drug and Food Control Administration (KDFCA). The registration departments in the KDFCA consist of five separate registration units: the pharmaceutical unit, herbal unit, veterinary unit, unclassified unit (borderline), cosmetics unit and food supplements unit. The herbal unit registers herbal teas, herbal coffees, homeopathic medicines and HMs. For an HM to be approved into the market, two main steps must be carried out: agent and company registration, and HM registration. Because all HMs in Kuwait are imported from other countries, the first step 'agent and company registration' involves the manufacturing company appointing a local agent to represent the product in Kuwait. This process is a one-off procedure required for the registration of all products. Moreover, the company registration requires the submission of an original and legalised Good Manufacturing Practice (GMP) certificate and a manufacturing licence from the health authority of the product's country of origin. In the second step, 'HM registration', the agent must submit a sample of the product and a dossier containing documents required for the registration of HMs in accordance with Ministerial Decree 201/9. The dossier must contain an original and legalised Certificate of Pharmaceutical Product or Free Sale Certificate, patient information leaflet, artwork of the finished product outer pack and label, original proposed price certificate authenticated by the Kuwaiti Embassy in the country of origin, toxicological and clinical studies or evidence of acknowledged scientific references, certificate of analysis of finished product and full stability studies. All products under the herbal unit must be analysed in the KDFCA quality control (QC) laboratory prior to their marketing. The QC tests depend on the certificate of analysis of the finished products that the agent provides in the initial submission of the dossier. This certificate is used to compare the specifications on the certificate with the QC analytical results. Currently, there are 191 HMs registered under the herbal

unit at the KDFCA. Further relevant products are registered under the unclassified and food supplement units, but there is no clear or current database of these. Kuwait imports the majority of its HMs from India, USA, Germany and the UK (see **Figure 4.1**).

Figure 4.1 Proportion of imported registered herbal medicines at the herbal unit in the Kuwait Drug and Food Control Administration with countries of origin. (Source: Kuwait Drug and Food Control Administration Herbal Registration Department)



UAE United Arab Emirates

The regulatory status of HMs varies from one country to another [26]. Depending on certain factors, where a HM may be defined as a functional food or a dietary supplement in one country, it may be defined as a herbal or a conventional medicine in others. This results in HMs imported into Kuwait being registered under different units in the KDFCA, as the allocation is not based on the nature or characteristics of the product itself, but its regulatory status in the country of origin.

Because of the lack of a clear definition of what constitutes an HM and a classification and registration system for HMs in the KDFCA, the registration process is uncoordinated. Consequently, some HMs are registered under the unclassified unit as dietary supplements or as functional food under the food supplements unit, both requiring few and less stringent requirements for registration. These units do not require the submission of safety studies or scientific references and not all products are analysed in the laboratory prior to their marketing. As a result, some products are marketed with poor quality and safety, resulting in safety issues for the public's health.

This is evident in the case of a young Kuwaiti girl who died after consuming registered herbal diet pills, which resulted in a heart attack and liver failure [6]. It is therefore important to establish a clear classification of HMs in the KDFCA structure, to allow a standardised approach for evaluating the safety, efficacy and quality of HMs imported into Kuwait.

In his book 'Public Policymaking', Anderson proposes that the policymaking process is a cycle with functional activities consisting of five steps [9]: (1) identify problem, (2) formulate options, (3) state contents of selected option, (4) implement option and (5) evaluate outcome of implemented option. He suggests that the policy steps are a workable approach to the analysis and study of policymaking with a scientific and academic approach. Having identified the problem, namely the absence of a classification and definition for imported HM registration in the KDFCA, for the second step (formulation of options), the authors reviewed relevant literature on policy implementation particularly with regard to HM regulations. However, limited documentation was identified on concepts from existing policies of other countries on how HM classifications were developed and implemented into their drug regulatory authority's (DRA) system. Furthermore, despite World Health Organisation efforts in producing international guidelines and consensus on HMs [10–19], countries continue to face difficulties in the implementation of HM regulations, owing to their diversity and complexity [20]. In the context of a wider project to inform a HM registration system in Kuwait, the aim of this article is to investigate the existing laws of DRA classification and definition of HMs in five countries and to illustrate a comparison.

4.2 Materials and Methods

4.2.1 Country choice

Generally, countries were selected for this comparison because they either have established registration processes and are major source countries for HMs imported into Kuwait (Germany, the UK and USA (**Figure 4.1**) or are countries similar to Kuwait in geographical proximity or size and approach (United Arab Emirates (UAE) and Kingdom of Bahrain). In countries within the European Union (EU), in this case Germany and the UK, the regulation of HMs falls within the scope of European Directive 2004/24/EC, which obligates the marketing of each product to be granted, based on rigid legislation for all EU countries. However, the EU directive guides

implementation in each country's own law; therefore, there may be differences in the implementation of Directives [21]. We chose Germany and the UK because of the differences between the two. Germany has a very well-established HM registration system in place that predates EU legislation and approximately 70% of German physicians have confidence in prescribing HMs to their patients [22]. Conversely, the UK introduced a system for HMs relatively recently based on the EU Directive.

In USA, the current pharmaceutical medicine regulatory system is acknowledged internationally as the gold standard for drug safety and efficacy [23]. However, there have been numerous criticisms about the regulation of dietary supplements and whether the regulation of HMs as dietary supplements is sufficient in USA [1, 24, 25]. USA is the major market for the pharmaceutical industry in which approximately 20,000 HMs are available in USA alone [24] with an estimated value of US $62 billion, which the World Health Organisation expect will increase to US $5 trillion by 2050 [26].

In UAE and the Kingdom of Bahrain, about 90% of pharmaceutical products are imported from abroad [27]. The regulation of pharmaceuticals in these countries is harmonised in view of their special relationship, geographic proximity, similar political systems based on Islamic beliefs and common objectives, ensuring a joint management of the safety, quality and efficacy of medicines. Therefore, the Kingdom of Bahrain and UAE were included in this country comparison. India has been excluded, despite being the largest source country of HMs imported into Kuwait, as the published literature indicates essential regulatory processes in the Indian HM registration system are found to be lacking, with existing legislation containing loopholes and being weakly implemented [28–30].

4.2.2 Data collection and analysis

We used document analysis, which is a systematic form of qualitative analysis requiring official documents to be reviewed and interpreted by the researcher to give meaning to an assessment topic [31]. Official law documents of HM registrations were identified from the five countries' competent DRA websites: UK Medicines and Healthcare Products Regulatory Agency [32, 33]; Federal Institute for Drugs and Medical Devices Germany [34]; US Food and Drug Administration (FDA) [35];

Department for Pharmacy and Drug Control UAE [36]; and Bahrain National Health Regulatory Authority [37]. Inclusion and exclusion criteria used for the data search in each regulatory authority website are presented in **Table 4.1**.

Table 4.1 Inclusion and exclusion criteria for data used in the document analysis

Inclusion criteria	Exclusion criteria
Available in English or Arabic	Language other than English or Arabic
Herbal preparations that are manufactured industrially in which the active ingredient(s) is/ are purely and naturally original plant substance(s) which is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product	Other types of preparations including homeopathic products, cosmetics, medical devices and conventional medicines including conventional medicines that contain herbal substance(s) as active substance(s) which has been synthesised or chemically altered Herbal products as teas or coffees
Herbal preparations that are used for treating/ curing purposes or supporting/improving body functions	Herbal preparations that do not have a therapeutic effect and are used as flavours or additives or have a cosmetic effect
Herbal preparations for human use only	Herbal preparations for animal use
Herbal preparations that are in a packed form	Raw unpacked herbs
Premarketing registration of Herbal products [initial registration]	Renewal of registration, amendments and cancelation of herbal medicines (HMs) Post marketing handling and control of HMs
HMs registration for the consumption of the general public	HMs as parcels for personal use HMs for the purpose of supplying to patients by herbal practitioners following a one to one consultation

HMs herbal medicines

The selection of data started by searching through each country's DRA website. The illustration of data categories or 'themes' could not be separated from the data selection phase. Because our aim was to inform policy design and implementation for a classification and definition for HM registration in Kuwait, the first category of choice was the definition of an ''authorised industrially manufactured therapeutic herbal product for registration'', which is associated with the registration pathways in each country's DRA. The second category was the main technical registration requirements that ensure the product's safety, quality and efficacy. A subcategory 'label requirements' was added, as it is an essential element for marketing a HM in some countries. The third category concerned how HMs are classified in each DRA. This category consists of factors that guide the classification decisions for the

registration pathways and requirements in each DRA; the presentation of the product and the purpose for which it is administered.

Data selected were extracted into a Microsoft Excel spreadsheet, analysed for similarities and differences across the countries within each category, and presented in a comparison table. The terminology used to describe (herbal) medicines in one country is different in another country; therefore, to maintain consistency in the comparison procedure, where appropriate, the authors have described the ‘‘authorised industrially manufactured therapeutic herbal product for registration’’ as ‘‘HM’’.

4.3 Results

4.3.1 Definitions and pathways

Table 4.2 summarises the definitions of HMs in each of the investigated country’s DRA. Under each definition, DRAs divide the product into different pathways for registration according to specific laws. All comparative authorities in their definitions state that HMs consist of substances of plant materials. The UK, Germany, UAE and the Kingdom of Bahrain have the highest resemblance in defining HMs, also defining a preparation. The UK and Germany use the term herbal medicine to describe HMs. USA uses the term botanical preparation, the UAE uses the term product derived from plant origin and the Kingdom of Bahrain uses the term herbal product.

Each of the authorities analysed divided HMs into one of two registration pathways. Registration pathways in the UK and Germany are traditional herbal registration (THR) or marketing authorisation (MA); in USA, dietary supplement or botanical drug; in UAE, traditional herbal medicine (THM) or herbal medicine; and in the Kingdom of Bahrain, health product or medicine.

In the UK, Germany, UAE and the Kingdom of Bahrain, the registration pathways offer a simplified registration for HMs, where instead of full registration as a medicine (i.e. requiring an MA and proven clinical efficacy), plausible efficacy as a result of established traditional use is sufficient (simplified registration); THR in the UK and Germany; THM in the UAE and health product in the Kingdom of Bahrain. A manufacturer can still register a medicine containing only herbal ingredients as any other allopathic medicine, which means stricter requirements with regard to evidence of efficacy (strict registration); MA in UK and Germany, registration of HM in the

UAE and the registration of a medicine with a vegetable substance in the Kingdom of Bahrain. USA differs from the other comparative authorities in that the traditional use pathway does not exist, instead, the product can be categorised under the dietary supplement pathway where products do not get assessed or registered prior to their marketing, which is in accordance with the Dietary Supplement Health and Education Act of 1994. The second pathway in USA involves registering the HM as a botanical drug (strict registration), which requires scientific evaluation and review by the authority prior to marketing.

Table 4.2 Summary comparison of herbal medicine (HM) definition and its regulation pathways in the drug regulatory authority systems of the UK, Germany, USA, United Arab Emirates (UAE) and Kingdom of Bahrain

	Regulatory Authority				
	UK	**Germany**	**US**	**UAE**	**Bahrain**
Definition	"A product is an **herbal medicine** if the active ingredients are herbal substances and/or herbal preparations only." "The herbal substance being processed can be reduced or powdered, a tincture, an extract, an essential oil, an expressed juice or a processed exudate." "A herbal preparation is when herbal substances are put through specific processes which include extraction, distillation, expression, fractionation, purification, concentration and fermentation."	"**Herbal products** are **medicinal products** which exclusively contain as active substances, either one or more herbal substances, one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh". "Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system". "Herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates."	"**Botanical preparations** consist of vegetable materials, which include plant materials, algae, macroscopic fungi, or a combination of these materials. Botanical preparations often have unique features, for example, complex mixtures, lack of a distinct active ingredient, and substantial prior human use." "Dietary supplement is a product other than tobacco intended to supplement the diet: a vitamin, a mineral, herbs or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or a combination of any of the aforementioned ingredients."	**"Product derived from plant origin** is a finished labelled medicinal product that contains as active ingredients aerial or underground parts of plants, or other plant materials or combinations thereof, where in the crude state or as plant preparations intended for prophylactic or therapeutic or other human health benefits." "Plant preparations are herbal ingredients present in a form other than the crude medicinal plant material including powdered plant material, balsams, dried and fluid extracts, tinctures, essential oils etc., prepared from plant material, and plant preparations obtained by fractionation, purification or concentration, without chemically defined isolated constituents regardless of whether or not its therapeutically active constituents have been identified."	"**Herbal product** contains as active substances herbal substances or herbal preparations, alone or in combination". "A herbal substance is whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh". "A herbal preparation is obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates."
Registration pathways	**THR (traditional use)** with directive 2004/24/EC Or **MA (conventional)** with directive 2001/83/EC	**THR (traditional use)** with directive 2004/24/EC Or **MA (conventional)** with directive 2001/83/EC	**Dietary supplement** with DSHEA of 1994 (does not get registered) Or **Botanical drug** with Federal Food, Drug and Cosmetic Act	**THM (traditional use)** Or **Herbal medicine** with Ministerial decree No. 3276/1997 for registration and re registration of products derived from natural source	**Health product (traditional use)** with decree amendments by law no (20) of 2015 Or **Medicine with vegetable substance** with decree by law No. (18) of 1997

DSHEA Dietary Supplement Health and Education Act, *MA* marketing authorisation, *THM* traditional herbal medicine, *THR* traditional herbal registration

4.3.2 Main registration requirements

Table 4.3 summarises the main registration requirements for assessing HMs in each of the investigated country's DRA. Under all registration pathways included in this study, apart from the dietary supplement pathway in USA, the authorities require the submission of evidence of GMP and QC tests for quality, bibliographic data or toxicological tests for safety, and evidence of traditional use or clinical studies for efficacy. In the dietary supplement pathway in the USA regulatory authority, products do not require registration; however, if it is a dietary supplement that contains a new dietary ingredient (NDI), the manufacturer must notify the authority and the notification must include evidence that the NDI is safe. An NDI means a dietary ingredient that was not marketed in USA as a dietary supplement before 15 October, 1994. All dietary supplements sold before 1994 were considered safe and could remain on the market without the need to file an NDI notification. The manufacturer may choose to market the dietary supplement even if the FDA indicated that the NDI notification was unsatisfactory. Although dietary supplements do not undergo assessment or registration, the FDA compels that a disclaimer must be added to the products showing that the FDA has not evaluated the product, the product is not intended to diagnose, treat, cure or prevent any disease and it should clearly state that it is a dietary supplement.

In the UK and Germany, as part of the EU harmonisation under Directive 2004/24/EC, the THR (simplified) pathway was established to create a simplified registration procedure for all traditional HMs not fulfilling the requirements for the MA (strict) pathway under Directive 2001/83/EC. Directive 2004/24/EC substitutes the requirement for medicines to have undergone randomised controlled trials with a clause of traditional use that includes evidence of 30 years of safe use; at least 15 years of which must be within the EU, to demonstrate plausible efficacy. Directive 2001/83/EC is still in use and the simplified procedure should be used only where no MA can be obtained. The regulatory authorities in those countries also require that the manufacturing company must include a statement and/or a mark clearly showing that the product is traditionally used.

Table 4.3 Summary comparison of herbal medicine (HM) main registration requirements in the drug regulatory authority systems of the UK, Germany, USA, United Arab Emirates (UAE) and Kingdom of Bahrain

Main registration requirements	Regulatory Authority				
	UK	**Germany**	**US**	**UAE**	**Bahrain**
Evidence of quality	GMP standards and QC tests for THR and MA	GMP standards and QC tests for THR and MA	Not required for dietary supplements GMP standards and QC tests for botanical drugs	GMP standards and QC tests for traditional herbal medicines and herbal medicines Declaration of pork-free contents Declaration of alcohol content	GMP standards and QC tests for health products and medicines with vegetable substance Declaration of pork-free contents Declaration of alcohol content
Evidence of safety	Bibliographic data for THR Toxicological tests for MA	Bibliographic data for THR Toxicological tests for MA	Not required for Dietary supplements unless it is a NDI Toxicological tests for botanical drugs	Bibliographic data for traditional herbal medicines Toxicological studies for herbal medicines	Bibliographic data for health products Toxicological studies for medicines with vegetable substance
Evidence of efficacy	long tradition of use for at least 30 years (Including. 15 years in the EU) for THR Clinical studies for MA	long tradition of use for at least 30 years (Including. 15 years in the EU) for THR Clinical studies for MA	Not required for dietary Supplements Clinical studies for botanical drugs.	Copies of at least two traditional herbal references for each herbal ingredient for traditional herbal medicines Clinical studies for herbal medicines	Copies of published scientific literature or international monographs for health products Clinical studies for medicines with vegetable substance
Label requirements	For THR: must include a statement that the product is exclusively based on long- standing use Must include a Certification Mark [THR]	For THR: must include the words "traditional medicines" and "traditionally used"	For dietary supplements: must include a disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" Must state on the label that it is a dietary supplement	No requirements	No requirements

EU European Union, *FDA* US Food and Drug Administration, *GMP* Good Manufacturing Practice, *MA* marketing authorisation, *NDI* new dietary ingredients, *QC* quality control, *THR* traditional herbal registration

Similarly, in the UAE and the Kingdom of Bahrain, submission of copies of bibliographic published scientific references for traditional use is sufficient for proving the product's safety and efficacy and accordingly the product would be eligible for the simplified registration pathway. In addition, being Islamic countries, both countries have passed similar laws requiring that medicines including herbals must be free from any pork materials, and if a product contains any alcohol, a declaration of alcohol percentage must be submitted along with specifying the reason.

4.3.3 Classifications

For a HM to be assessed and evaluated under the appropriate registration pathway, HMs in the study authorities are classified according to two key features or characteristics; the presentation of the product and the purpose for which it is administered (**Table 4.4**). In all the comparative authorities, the medical claims and the preparation type affect the product classification under the two registration pathways in each regulatory authority. The strictest registration pathway is applied to products with medical claims of curing and treating diseases.

In the USA regulatory authority, dietary supplements are only allowed in oral preparations, all other preparation types are classified under botanical drugs, which require the strictest registration requirements. In comparison, the UK, Germany, UAE and the Kingdom of Bahrain regulatory authorities, the traditional (simplified) registration pathway may include other preparations that can be administered externally but not by injection. In the UK, Germany and the Kingdom of Bahrain regulatory authorities, if the herbal product requires a medical prescription or practitioner, the product is automatically classified in the pathway that requires the most strict registration requirements; i.e. requiring MA.

Table 4.4 Summary comparison of herbal medicine (HM) classification factors under the different pathways in the drug regulatory authority systems of the UK, Germany, USA, United Arab Emirates (UAE) and Kingdom of Bahrain

Classification factors	Regulatory Authority				
	UK	**Germany**	**US**	**UAE**	**Bahrain**
Presentation	If a claim to treat major health conditions is added, the product is classified as a medicine that requires MA. If a therapeutic indication based on long-standing use is added, the product is classified as medicine that require THR. THR products can only be presented as oral, external and inhalation preparation. MA products may include any preparation type.	If a claim to treat major health conditions is added, the product is classified as a medicine that requires MA. If a therapeutic indication based on long-standing use is added, the product is classified as medicine that require THR. THR products can only be presented as oral, external and inhalation preparation. MA products may include any preparation type.	For a product to be classified as a dietary supplement, only function and structure claims are allowed. Products that include claims of treating, diagnosing, preventing or curing diseases are automatically classified as botanical drugs. Dietary supplements are only allowed in oral preparations. Botanical drugs can be presented in any preparation.	Products that include medical claims are classified as herbal medicines. If a product uses traditional use claims, it is classified as a traditional herbal medicine. Traditional herbal medicines can be presented in an oral, topical and rectal formulations only. Herbal medicines can be presented in any preparation.	Product that contains claims based on traditional use are classified as health products. If a medical claim to cure, treat or prevent a disease is added on the label, the product is classified as a medicine with vegetable substance. Health products can only be presented as oral, topical and nasal formulation. Medicines with vegetable substance can be presented in any preparation.
Purpose	If a product requires the supervision of a medical practitioner, or a medical prescription, the product is classified as a medicine that requires MA.	If a product requires the supervision of a medical practitioner, or a medical prescription, the product is classified as a medicine that require MA.	Not specified.	Not specified.	Product that contains substance that supply on a medical prescription is classified as a medicine with vegetable substance.

MA marketing authorisation, *THR* traditional herbal registration

4.4 Discussion

This study compared the similarities and differences between the current HM registration systems of five countries, indicating diversity in the classification of HMs including terms used, definitions, type of licence, requirements, restrictions and preparation type. Comparing the five countries, the UK, Germany, UAE and the Kingdom of Bahrain have applied a reasoned and more structured approach to registering HMs. USA differs from these four countries in two important aspects.

First, the marketing of HMs. The regulation of HMs in USA differs considerably from that in UK, Germany, UAE and the Kingdom of Bahrain. In USA, when HMs are regulated under the dietary supplements pathway, along with vitamins, minerals and other nutritionals, they do not undergo pre-marketing safety evaluation by the FDA. Conversely, HMs marketed in the UK, Germany, UAE and the Kingdom of Bahrain must adhere to pre-marketing HM registration laws and registration requirements including specific laboratory, manufacturing and storage standards. The FDA's intervention with dietary supplements does not begin unless the product enters the market and is proven to have a significant risk to the consumer. A study conducted by the National Institutes of Health found that 15.5% of US hepatotoxic events were associated with the consumption of dietary supplements and herbal products [38]. In another study conducted in 2013 by researchers in Toronto who analysed 44 herbal supplements sold in both USA and Canada, it was revealed that less than half the supplements contained any herbal substances mentioned on the label and more than half the analysed supplements contained additional ingredients that were not on the label [39]. The assessment of safety has therefore become more challenging in USA as a result of the type of regulation used [40]. While regulating HMs as dietary supplements increases the availability and variety of many products for the consumer, the lack of registration and assessment of such products can be a major disadvantage for consumer safety.

Second, registration requirements for HMs. In USA, if a claim to treat or cure a disease is added to the label of a dietary supplement, the product will be regarded as a drug and require assessing and registering prior to marketing. This classifies the product under the botanical drug pathway and the same rigorous requirements and standards of conventional drugs apply, including the evidence of clinical studies. As a result, the FDA received over 400 botanical drug applications between 2004 and 2013,

in which only two have so far received the FDA approval [41]. On the contrary, the UK, Germany, UAE and the Kingdom of Bahrain established simpler registration requirements based on traditional use as evidence of efficacy existing. This ensures that the efficacy of traditional herbal medicinal products is considered plausible without the need for conducting extensive clinical studies. In Germany and the UK, as per the regulatory harmonisation of EU member states under the latest Directive 2004/24/EC, HMs registered by one member state shall be accepted automatically by other member states. The new policy provides public health benefits to those countries that did not have such legislation previously. The directive obligates that the members' health authorities must also perform a premarketing product quality and safety check. Therefore, this legislation may reduce the risk that unsafe HMs will enter the market [42].

Overall, because HMs imported into Kuwait are registered according to the product's status in the country of origin, a major challenge is the inconsistency in the definition of a HM across the international DRAs. This explicates the uncoordinated registration process in the Kuwaiti DRA, which results in some unevaluated products, for example, imported dietary supplements from USA, being registered under units with insufficient evaluation measures.

A reasonable anticipated step would be the possibility for all international DRAs including Kuwait to adopt a universal harmonised definition of what constitutes a HM for the purpose of registration that would guide the product into the most appropriate conformity assessment. A proposed definition could be: herbal preparations made from one or more herbs as the active ingredients, which may additionally contain excipients; however, finished products to which the active substance has been chemically altered or added, including synthetic compounds and/or isolated constituents from herbal material, are not considered herbal [43]. Such a clear definition would also allow a standardised regulation, which could ensure that all HMs approved for sale are safe on a global scale, especially with USA being one of the world's largest exporters for HMs. In Kuwait, in addition to adopting a universal definition for HMs, a directive should also be specified that all products that match the proposed definition must be assessed under one department (the herbal unit). This is to prevent HMs from being categorised as dietary supplements, which as a result circumvent the detailed assessment procedure of the KDFCA. Moreover, in the process of improving HM legislation, the KDFCA will need to consider carefully how

to regulate products imported from countries where regulations are very loose or do not exist.

This study has some limitations, the main one being the decision of disqualifying India despite their existing HM regulations, which has led us to neglect a major source country for HMs in Kuwait. However, this study focused on gaining insights of international, well-established, competent health regulatory systems to inform a robust HM registration system in Kuwait, and evidence indicating the absence of essential regulatory processes in the Indian HM registration system and weak implementation of the current legislation [26–28] required the exclusion of India as a competent DRA. Another limitation is that the findings of the study were limited to the information available on each country's DRA website. Therefore, to be consistent, it has only been possible to analyse and compare the data available in all DRAs together and was not always possible to compare all countries across other aspects that may not be publicly available. For example, guidelines or standard operating procedures for the classification of HMs. Despite the limitations, the study provided an international classification reference and recommends a definition for HM registration for Kuwait and other countries that do not currently have such laws implemented.

4.5 Conclusion

Some jurisdictions allow an additional less stringent registration process for HMs, which permits efficacy to be plausible as a result of traditional use, while others, USA in particular, do not. Consequently, many such products escape sufficiently rigorous review as they are instead marketed as dietary supplements. This needs to be considered in designing or updating registration systems in countries such as Kuwait, which import such products and assess these in the light of their regulatory status in their country of origin. Because of the heterogeneity in other countries' definitions, it will be essential for Kuwait to clearly define what constitutes a HM and require that all relevant products be reviewed in one unit to prevent any being misinterpreted as dietary supplements.

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Conflict of interest Azhar H. Alostad, Douglas T. Steinke and Ellen I. Schafheutle have no conflicts of interest directly relevant to the content of this study.

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5 Chapter Five: Study Two

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Medicine Policy Implementation in Drug Regulatory Authorities: a Review of the Literature

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Abstract

Background

Because of the differences in how countries regulate herbal medicines (HMs), their regulatory control can be more challenging than for conventional medicines. For the purpose of informing a HM registration system and its implementation in Kuwait, which does not manufacture but import all HMs and assesses them according to the regulations in their country of origin, the aim of this study was to review published research investigating the implementation of medicines policies and regulations including herbals.

Methods

Three databases were used to search for peer-reviewed papers published in English up to February 2019. Thematic analysis was performed by categorising factors affecting medicines policy implementation as either facilitators or barriers under four determinants; political, resources, actors, and cultural determinants. Methodological assessment was also performed to evaluate the quality of included papers.

Results

A total of 11 papers were included, none of which investigated HMs policies. Analysis identified 15 facilitators and 25 barriers which related to the political, resources and actors, with little attention paid to cultural aspects. Quality assessment of included papers showed that the majority of papers had methodological weaknesses such as limitations in data collection, lack in clarity about data analysis, lack in the use of theories and frameworks to guide interpretation, and limited contextualisation of findings.

Conclusions

Further high quality context specific empirical research is needed to guide effective medicines (particularly herbals) policy design and implementation in countries like Kuwait, which does not produce its own products but assess products registered elsewhere. Nevertheless, this study provided general practical recommendations which countries can use to prepare for future implementation.

5.1 Background

Among medicines, herbal medicines (HMs) account for about 20% of the overall drug market, and a population of more than 1.5 billion consume them worldwide [1]. The perception that because HMs are natural they are safe, is untrue [2]. Like conventional medicines, HMs have therapeutic effects and therefore could produce side effects varying from nausea, allergies, psychiatric symptoms, liver and kidney toxicities, and even death [3-6]. Presence of high toxic heavy metal content and adulteration of some HMs with prescription drugs have also been reported in the literature [7]. Having adequate policies and regulations in place helps assure consumers of HMs safety [8].

Registration of medicines, also known as medicine licensing or marketing authorisation, is a significant aspect of medicines policy and regulation. The ultimate goal of the regulation is to protect the public's health by scientifically evaluating and analysing medicines in the national drug regulatory authority (DRA) of a country prior to their entry into the market in that country, to ensure that all products meet the standards of quality, safety and efficacy [9]. However, these criteria are not applicable in the same way to herbal products that are industrially manufactured, consisting of active ingredients that are pure plant materials, which are not chemically altered, and are responsible for the overall therapeutic effect of the product [3, 10, 11]. There is no global consensus in terminology for the category of such products [12], therefore for the purpose of this study, the term HMs will be used to refer to products matching this description.

The regulatory control applied to HMs and their assessment for quality, safety and particularly efficacy differs between countries [4]. Depending on how countries define HMs, a single HM may be classified as a dietary supplement, traditional herbal medicine, or even a conventional medicine [13]. For example, St. John's wort (*Hypericum perforatum)* which is commonly used for managing mild depression, is registered as a dietary supplement in the United States (US) [14], as a traditional herbal registered product in the United Kingdom (UK) [15], and as a prescription only medicine in Ireland [16]. Regulatory requirements to assess the quality of HMs are usually easier to obtain than requirements to assess safety and efficacy. For example, in most countries, manufacturers are required to conform to good manufacturing practice (GMP) throughout the manufacturing, packaging, labelling, and storing process to demonstrate the quality of HMs [13, 17]. However, due to issues related to

the financing, ethics, product standardisation and the design of clinical trials concerning HMs, many HMs do not undergo clinical trials, and therefore manufacturing companies are unable to provide DRAs with clinical evidence to prove the product's efficacy [18]. Consequently, some countries such as the UK, under a European Union (EU) directive, offer a simplified registration for HMs called the traditional herbal registration (THR), where instead of a full registration as a conventional medicine (i.e. requiring a marketing authorisation and proven clinical efficacy), 'plausible efficacy' due to established history of traditional use is sufficient to assure efficacy, and evidence of bibliographic data or toxicological tests is sufficient to assure safety. In other countries, however, such as the US, the concept of traditional use does not exist; instead, the product can be categorised as a dietary supplement where no assessment or evaluation is required prior to marketing [13]. In the US, DRA intervention with dietary supplements does not begin until the product has entered the market and is suspected to have a significant risk to the consumer. Indeed, many studies have confirmed cases of serious organ toxicities linked to a number of HMs marketed as dietary supplements [19-22].

The above concerns, specifically serious adverse reactions, the lack of a harmonised definition and classification for HMs globally, and the insufficient regulatory control over HMs in some countries, has implications for (often small) countries with very limited pharmaceutical manufacturing capacity, which therefore rely partly or fully on importing rather than manufacturing or regulating their own HMs. One example of a country which imports all of its conventional and HMs is Kuwait, whose DRA lacks a clear definition and classification system for imported HMs. Therefore, imported HMs are not assessed based on their nature or characteristics, but based on the regulatory status in their country of origin. Consequently, the registration process is inconsistent, leading to products imported from different countries but sharing the same characteristics assessed differently [23]. Moreover, many HMs imported into Kuwait from the US [13] – due to their classification as dietary supplements - evade sufficiently thorough assessment, resulting in inadequate evaluation of these products, causing safety issues to consumers [23, 24]. It is therefore important to establish a clear HM definition and classification policy in the Kuwaiti DRA and other similar countries which rely heavily on imported medicines, to allow an adequate and consistent approach for evaluating the quality, safety, and efficacy of imported HMs.

Reforming a policy, such as the classification system for HMs, should be approached in a rational, rigorous and systematic way, using high quality, valid and reliable evidence [25-27]. Evidence-based policymaking produces well informed decisions about policies, programmes and projects by using the best available research evidence [28]. Policy researchers suggest exploring other countries' approaches and experiences of the policy in question as a useful approach to inform policy design [29, 30]. Therefore, in 2018, the authors performed a comparison of regulatory processes in countries with more advanced systems for HMs, to investigate their existing HMs definition and classification laws [13]. These countries are either major source countries for HMs imported into Kuwait (UK, Germany and US) or countries that are geographically, culturally and politically similar to Kuwait (United Arab Emirates and Bahrain). The study provided a clear and informative international HM classification, and recommended a definition for HM registration for importing countries, such as Kuwait.

However, policy development should not only be concerned with exploring policy content, but also with insights into policy implementation. Using published research evidence on policy implementation experiences in different countries can help understand factors that enhance (i.e. facilitators) or impede (i.e. barriers) policy implementation [31-33]. Therefore, as part of a wider project to inform a HM registration system in Kuwait, this study aimed to review published research which investigated the implementation of policies and regulations for medicines, including HMs, with a particular focus on factors affecting policy implementation success or failure.

5.2 Methods

5.2.1 Study design

The most common adopted model to policymaking is the stages heuristic model [33-35]. The model describe (i) the policy problem, (ii) how the policy is formulated, (iii) how the policy is transferred into practice, (iv) how potential policy change is integrated, and (v) how is it evaluated. Having described the problem in the introduction, and formulated options through a comparison of five advanced HMs systems in a previous study [13], the third stage is addressed in this study.

5.2.2 Inclusion and exclusion criteria

Inclusion criteria in this review consisted of peer-reviewed papers published in English, which are based on empirical research or have a clear empirical base (i.e. include at least one empirical data source), and focus on categorising, describing or explaining factors affecting implementation process of medicines policies or regulations in a DRA setting.

This literature review excluded experiences of countries that rely exclusively on medicines' donations, as policy implementation in self-sufficient countries that have financial control over the supply of their medicines differs from those in countries who rely on external donor funds, where for example, a lack of purchasing power may influence the experiences and results of policies implemented [36].

5.2.3 Data selection, extraction and analysis

The review was conducted in 2019, and involved a four step process adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37].

First, English-language peer-reviewed papers published until February 2019 were identified through PubMed, Web of Science and the International Bibliography of the Social Sciences, using a combination of relevant search terms: (medicine OR drug OR 'herbal medicine'); AND (policy OR regulation); AND (implementation OR analysis OR process); AND ('regulatory authority' OR 'medicine agency'). There was no restriction on publication date. Identified titles were screened and duplicates removed. Second, abstracts were screened and checked for relevance, and papers not meeting the inclusion criteria were excluded. Most exclusions in this stage were linked to the primary focus on policy implementation processes in settings other than DRAs, such as general health sector reforms (i.e. health insurance, health promotion, social care). Third, the remaining papers were reviewed in full to identify the final set of papers to include and analyse. At this step, most exclusions were linked to papers focusing on issues related to the consumption of medicines and HMs, papers focusing on the impact rather than process of implementing certain medicines policies (i.e. whether the policy was successful or unsuccessful), papers not based on empirical research such as editorial papers, opinion papers, organisation reports and papers

covering a largely theoretical orientation. Further papers were identified from the references of included publications.

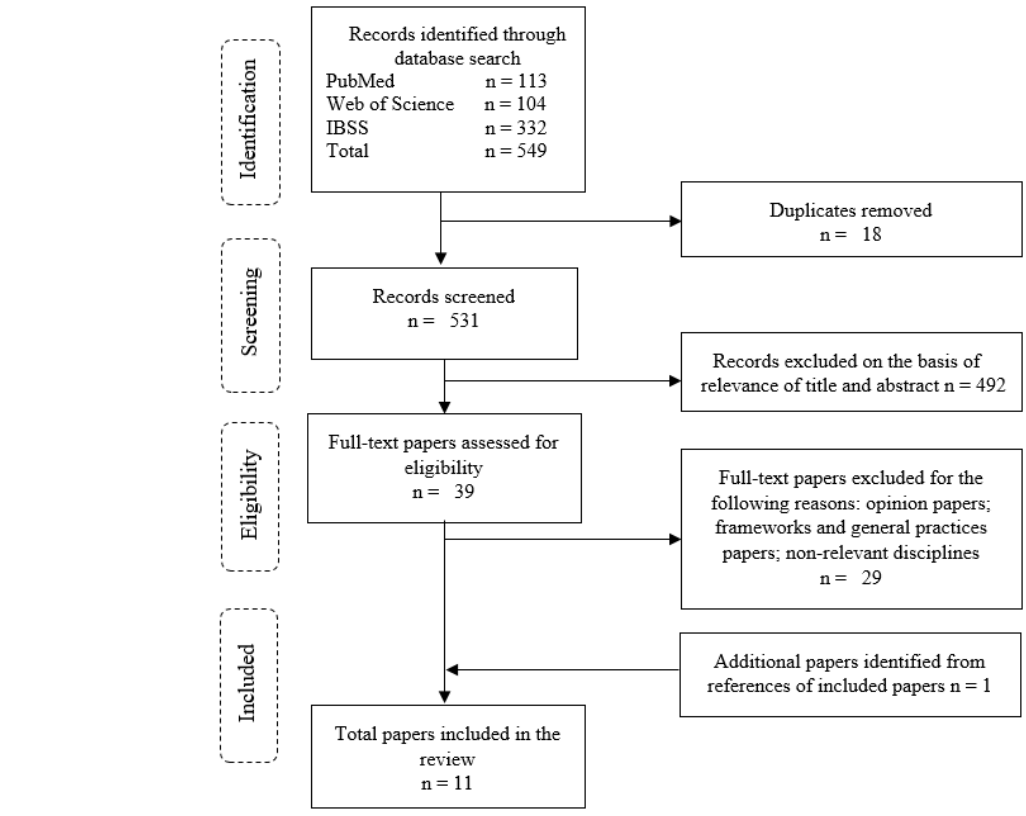
Fourth, the final set of papers were analysed by extracting data and placing them in a Word ® table. To extract data on factors influencing implementation, findings were coded as facilitators or barriers and counted by frequency. Coding the text with 'facilitator' or 'barrier', considered as any factor, characteristic, view or belief that either enabled or impeded implementation. The identified factors were then categorised following thematic analysis [38], enabling their synthesis to revolve around the same underlying matter. The construction of factors coded as barriers or facilitators were grouped under themes using Anderson's [39] four general determinants of policy implementation as a logical framework: (a) politics (i.e. how the implementation of policies is affected by governmental bureaucracy; their formal structure, procedural rules and functions), (b) actor's characteristics (i.e. how the implementation of policies is affected by the behaviour, values and desires of certain actors), (c) resources (i.e. how the implementation of policies is affected by financial, human and organisational resources), and (d) the organisation's culture (i.e. how the implementation of policies is affected by the habits and norms of the organisation in performing daily activities).

Data extraction and analysis also included mapping the papers' policy focus and assessing the quality of included papers, as not all published research is valid, reliable and relevant, and therefore synthesising evidence from literature must also include a quality assessment of considered papers [40]. Therefore, data were extracted on policy type, the country in which the policy was investigated, publication date, study aim, study design, data collection and analysis methods, type and number of subjects recruited, study setting, theoretical framework used, and type of results (e.g. descriptive or analytical). The criteria used in assessing the methodology of the studies were adopted from Mason [41], and Mays and Pope [42], and they were (i) clarity of research aim and appropriateness of design to fulfil aim, (ii) rigorous methodological approach (e.g. use triangulation, describe how interpretation was reached, explain the development of categories and concepts, include use of relevant theoretical or conceptual approach etc.), and (iii) display of sufficient data to support interpretation and conclusions.

5.3 Results

Figure 5.1 describes the flow of papers through searching and screening for inclusion. The search identified a total of 549 papers, of which 18 were removed as duplicates and 492 were excluded following screening of titles and abstracts. After fully reviewing the remaining 39 papers, 29 were excluded; 21 were not primary research and eight were not focusing on implementation process or factors affecting it. An additional paper was identified from references, and a total of 11 papers met the inclusion criteria for the thematic synthesis. For a detailed description of the characteristics and findings of the analysed papers, see Table 5.1 in Additional file 5.1.

Figure 5.1 Flow diagram of paper selection, adopted from PRISMA guidelines [37]



IBSS International Bibliography of the Social Sciences *n* number of papers

5.3.1 Papers' policy focus, and methodological and analytical rigour

Included papers were published between 1998 and 2017. None investigated HMs policies. Papers consisted of eight which investigated the implementation of specific conventional medicines policies; malaria treatment policy [43-46], opioids access policy [47, 48], human immunodeficiency viruses (HIV) treatment policy [49], tuberculosis access policy [50], two which investigated implementation of general conventional medicines policies; medicines registration, procurement and access [51, 52], and one which investigated pharmacovigilance policy [53].

Nine papers comprised of research that was conducted in low and middle-income countries (LMICs), with eight conducted in Africa; South Africa, Tanzania, Uganda, Ethiopia, Kenya, Malawi, Rwanda and Zambia [43-47, 49, 50, 52] and one conducted in Eastern Europe; Republic of Moldova [51]. Of these eight papers that investigated LMICs in Africa, two also investigated a LMIC in South America; Peru [46] and a LMIC in Asia; India [50]. Only two papers reported research conducted in high income countries (HICs) in Europe; Germany, Poland, Portugal, France and Finland [53], and the US [48].

Using quality criteria adopted from Mason [41] and Mays and Pope [42], findings are divided into a) research aim and appropriateness of design, b) approach to data collection c) approach to data analysis, and d) display of sufficient data.

5.3.1.1 Research aim and appropriateness of design

Although all except one paper [47] indicated either the paper's aim or objectives and/or research questions, most were outlined as descriptive aims or endpoints [44-46, 48, 49], with few aiming to assess and analyse implementation [51-53]. Most investigations were case studies, even though only seven papers identified them as such and explicitly discussed research design [43, 44, 46, 49-51, 53]. The most commonly adopted feature across the papers was the comparison of specific policy between different countries or areas [43, 46, 47, 50, 52, 53]. However, some of those papers had limited contextualisation of the experience they report [47, 53] or inadequate comparison and contrast of cases in analysis [46].

5.3.1.2 Approach to data collection

All papers stated clear data collection methods. The majority of papers (n= 8) used a qualitative approach for data collection, either by using a single qualitative method; interviews [45, 53] or focus group discussions [47], or by using a mixed set of qualitative methods ranging from interviews, focus group discussions, document review and media analysis [43, 46, 49-51]. Only three papers employed mixed methods data collection using a combination of quantitative surveys with qualitative interviews [44, 48, 52].

Although the population type was specified in all papers, clear sample justification and approaches were described in only six papers [43-45, 49, 50, 52]. In all papers, population samples were predominantly key officials involved in the policy process in a DRA (i.e. policymakers, managers and staff), except one paper, in which the population sample was mainly clinicians in private clinics that implemented a policy legalised by the DRA [48]. Of the papers that involved key officials from DRAs, seven also involved sellers from drug stores [44], staff from pharmaceutical companies [52], researchers and think tanks [45, 49, 52] and healthcare professionals such as nurses, pharmacists and doctors [47, 48, 53]. All papers except three [46-48] stated a clear sample size. In the research employing qualitative methods, five included a sample of 15-22 participants [43, 45, 49, 51, 52] and three included a sample of 30-89 participants [44, 50, 53]. In the papers reporting studies employing quantitative methods, sample size ranged from 30 [44] to 249 participants [52].

5.3.1.3 Approach to data analysis

The majority of the papers (n=8) provided limited or no detail on data analysis, with little or no attempt to categorise findings, offering a descriptive approach with minimal depth on the policy implementation process, factors influencing it, and reasons behind presence of certain factors [44-49, 52, 53]. Only three papers demonstrated an analytical approach with rigorous analyses by referring to theories and frameworks; using Walt and Gilson policy analysis model which explores a particular policy change considering the actors involved in the policy, policy processes, policy content and policy context [43], the World Health Organisation tool for the assessment of regulatory systems which identifies main gaps and progress by examining to what

extent technical aspects are implemented (such as strategic plans, training, post marketing etc.) [51], and the action-centred approach which involves using experiences of actors within social and organisational contexts at different levels of policy and implementation to understand the factors influencing the policy process [50].

5.3.1.4 Display of sufficient data

Most papers used documentary proof or general observations to illustrate findings about the factors that influenced policy implementation (n=7) [44, 47, 48, 50-53] rather than perceptions or experiences of participants involved in the implementation (n=4) [43, 45, 46, 49]. In six papers, the majority of findings provided a description of an intervention or a policy, with minimal insights into specific aspects that influenced implementation [45, 48, 50-53]. Just over half (n=6) of the papers presented factors that enabled and hindered implementation through process of policy change, providing experiences from different countries with incorporating the context and therefore explaining how and why different facilitators and barriers came into play in the implementation process [43, 45, 46, 48-50]. The remaining papers (n=5) did not investigate policy implementation as a change process and therefore only presented insights into issues and deficiencies in the implementation with limitations on reasons behind why such factors exist [44, 47, 51-53].

5.3.2 Reported facilitators and barriers

All papers reported either facilitators and barriers, or only barriers, of policy implementation. The synthesis identified 15 unique factors operating as facilitators and 25 as barriers. To interpret all the factors reported, facilitators and barriers were categorised into Anderson's determinants, namely, 'Political determinants', 'Resources determinants', 'Actors' determinants' and 'Cultural determinants'. Overall, the reported factors emphasised the political forces, technical resources and actors' characteristics, with little attention paid to cultural aspects. **Table 5.1** describes the reported facilitators and barriers categorised into themes. Below, the reported factors within each theme are described, supported with some supplementary information not mentioned in the table.

Table 5.1 Reported facilitators and barriers categorised into themes

Theme	Facilitators	Barriers
Political Determinants	Strong political commitment from government [43, 45, 49, 52] Political global pressure of international organisations and neighbouring countries [45-46, 50, 52]	Lack of political influence on research [43] Lack of official endorsement and sanctions [43-44, 52] Complex bureaucratic procedures [43- 44, 47-48, 52] Misuse of political power [47, 53] Political and economic changes [46, 49] Competing interests [46]
Resources Determinants	Adequate training for employees [43] Ongoing monitoring and supervision [43, 50] Using evidence from real world experiences [46] Involving researchers [43, 46] Expert support from international organisations [46]	Lack of training [43, 45, 47- 48, 53] Failure to use lessons from previous policies [43] Lack of standard operating procedures and guidelines [45, 47, 48, 51- 52] Low human resources [44, 46, 51- 52] Lack of sufficient funding[45- 47, 50- 53] Lack of time to introduce legislative changes [51, 53] Poor organisational capacity and infrastructure [45, 49] Lack of continuous research [45, 46] Lack of strategic plans for implementation [43, 47, 50] Lack of inspections and monitoring [44, 50] Lack of media exposure and awareness campaigns [53]
Actors' Determinants	Implementers' morality [43, 50] Leadership [43] Personalising the information on negative outcomes [43] Implementers' experiences [43] On-going problem solving through communication [46] Providing information on the exact date of implementation [43] Involving employees as part of the decision-making process [46]	Frequent change of power and leadership [47, 51] Lack of managerial support and involvement [45- 46, 52- 53] Lack of managers' knowledge [48, 51]
Cultural Determinants	Not reported	Relationships between inspectors and implementers [44] Lack of knowledge and interest in improvement [44- 47, 50] Culture of blaming [47] Inspections not perceived as duties [52] Inspections perceived as way of controlling staff [46] Disrespectable manners towards lower level staff [43, 53]

5.3.2.1 Political determinants

Political factors were discussed in three aspects; the formal legislative process, the geographical and economic situation of the country, and the power manoeuvres. Reported facilitators were linked to the first and second aspects and are characterised as the strong commitment from government to finalise policies in a timely manner [43, 52] especially within policies that have a direct effect on the health of the population [45, 49], and the pressure of international organisations and neighbouring countries on implementing a harmonised policy across countries with political connections [45, 46, 50, 52].

Similarly, a list of barriers related to the first and second aspects were reported, consisting of the complex bureaucratic procedures [43, 44, 47, 48, 52], which resulted in some interventions being implemented without official endorsement and sanctions [43, 44, 52], and the effect of the economic and global political changes on policy implementation budgets [46, 49]. Barriers related to the third aspect were reported as the misuse of political power to serve personal interests without considering the interest of the population [47, 53]. One paper reported that usage of research and evidence in such cases were neglected [43]. Another paper reported that the improvement of some policies were ignored as a result of competing interests across power stakeholders [46].

5.3.2.2 Resources determinants

Resources factors were discussed as technical aspects of the policy. Training of all key staff and managers on the principles, importance and methodology of policy implementation was reported as a key factor facilitating implementation in one paper [43]. In addition, involvement of researchers and experts from international organisations as part of the decision making process was reported as another important facilitator as the policy was based on scientific evidence, real world experiences which were usually concerned with uptake of health inequality research [43, 46]. The organisation's establishment of an effective monitoring and supervision system, and feedback on implementers' performance were also reported as facilitators to implementation which increased implementers' adherence and commitment [43, 50].

On the contrary, the absence of implementers' training [43, 45, 47, 48, 53], lack of inspections, follow-up and provision of feedback from implementers [44, 50]

were cited as barriers. In many papers, insufficient financial resources were reported as a major barrier to effective implementation [45-47, 50-53]. Absence of an implementation plan to allocate sufficient resources was reported in some papers as the main barrier to implementation [43, 47, 50]. Moreover, some papers reported failure to use lessons and evidence from previous policies [43], absence of technical tools such as standard operating procedures and guidelines [45, 47, 48, 51, 52], lack of continuous research and data sources to update policies after implementation [45, 46], and insufficient human resources to carry out implementation [44, 46, 51, 52] as barriers to implementation. One paper reported that lack of media support and campaigns that provide knowledge and awareness to consumers on the importance of complying with the policy, and lack of information on the safety issues that would arise as a result of noncompliance, was another important barrier to implementation [53].

5.3.2.3 Actors' determinants

Actors' factors were discussed as the staff, managers and decision makers' characteristics and involvement. Facilitators of implementation described in this category included commitment of all actors, and effective coordination such as on-going problem solving [46], managerial support [43], and clear and convincing explanation on the importance of compliance through personalising information on negative outcomes [43]. Availability of a dedicated and permanent chairperson [46], staff professional experiences and skills, their involvement in the policymaking process and informing affected parties of the exact date of implementation to ensure readiness were also reported as important implementation facilitators [43].

Similarly, a number of barriers related to leadership and coordination were reported, consisting of frequent change in leadership [47, 51] and lack of involvement of managers [45, 46, 52, 53] resulting in poor compliance with the policy as no support and follow-up mechanisms were in place to secure compliance. Two papers also reported the lack of managers' knowledge and expertise to manage a new implementation [48, 51] as an important barrier to implementation.

5.3.2.4 Cultural determinants

Few papers reported on some sociocultural factors, acting only as barriers. These included a culture of blaming and fear on the presence of staff in higher rank [47],

staff punishment, and disrespectable manners of managers towards lower level staff [43, 53]. A number of papers also reported the lack of managers in providing staff with some form of recognition such as expressing gratitude and appreciation or monetary incentives as one of the barriers to effective implementation [44-47, 50]. Other barriers included the way of monitoring and inspection perceived as a way of controlling staff [46], unprofessional relations between inspectors and staff [44], and inspections not perceived as duties [52] resulting in staff not being consistently monitored.

5.4 Discussion

This study aimed to identify and critically appraise published research on medicines policy implementation processes (including HMs), with a particular focus on facilitators and barriers to effective policy implementation. Restricting studies to those undertaken in financially independent countries (and thus excluding those relying on donations), the review identified 11 studies which met the inclusion criteria, with no papers investigating HMs policies. The relatively small number of published papers in this area, and the recency of their publications, are not surprising, as previous health policy and planning research has explained that the area of policy research is new, and critically, the ability to access the policy environment and conduct meaningful research requires engaging with policy leaders and investigating sensitive issues, limiting the ability to ask certain questions [54, 55]. Moreover, the review revealed that the majority of papers focused on implementation experiences within LMICs in Africa and Asia, which investigated medicines treating life threatening diseases (malaria, tuberculosis, HIV), with few papers investigating experiences from HICs in Europe and the US. More importantly, despite the broader implementation science literature emphasis on the effect of the organisational culture such as the members' beliefs, values, behaviour and norms to shape the way that policy reforms are put into action [56-58], this review identified very few papers exploring the cultural challenges and only in little depth. More empirical efforts are required to identify, interpret and synthesise evidence on organisational culture and its influence on its members when implementing medicines policies. This is important because the members are the foundation of change, and it is they who will either welcome or resist it [59].

Many of the included studies had analytical weaknesses. First, the depth of data presented, and even collected, was often limited, and papers commonly did not

provide clarity about their analytical approaches and provided little commentary or reflections on the interpretations made. Second, most papers were descriptive, and lacked an explicit explanatory focus. Therefore, the majority of analyses can be classified as "of policy" rather than "for policy", as they did not seek to assist future policy-making, neither did they discuss challenges to bringing about policy change. Only a few papers presented factors that enabled and/or hindered implementation through the process of policy change, providing experiences with incorporating the context and therefore explaining how and why different facilitators and barriers came into play in the implementation process. Third, while papers identified barriers and/or facilitators to policy implementation, theory or framework were rarely used to guide interpretation and understanding. This issue has been noted as common in similar reviews of health policy research which identified that poor theoretical underpinning made it difficult to understand and explain how and why implementation succeeded or failed [60-62]. This therefore limited opportunities to identify factors that predict the likelihood of implementation success and develop better strategies to inform policies. In informing policy design, it will be useful for researchers to incorporate a systematic approach to policies investigated, developing clear and empirical suggestions about the issue they are investigating within an explicit framework. Explicit use of theory and framework would further help researchers from many disciplines to easily utilise the findings and build on each other's work.

A number of widely used frameworks and theories of the policy process exist [36, 61]. To promote the use of such frameworks, in this review, Anderson's determinants of policy implementation was adopted as a useful and simple way that helped situate implementation research within the wider framework of the policymaking heuristic stages. The framework provided a useful mechanism for structuring and interpreting the study findings and has several advantages. First, it centres attention on the officials and organisations who make and implement policy decisions, and the factors that influence and condition their actions. Second, additional determinants can be introduced if experiences indicates that they would strengthen description and analyses. Third, the framework can incorporate different types of data collection and analysis, whether historical, legal, or normative, and can be used to study a single policy, or to compare the implementation of several policies. Fourth, the framework is not culturally related, which means that it can be used to study implementation factors of systems in different cultures. Other types of determinant

frameworks reported in the literature which researchers can adopt include: the Active Implementation Frameworks [63, 64], Understanding-User-Context Framework [65], Conceptual Model [66], framework by Grol et al. [67], framework by Cochrane et al. [68], framework by Nutley et al.[69], framework by Ferlie and Shortell [70], Theoretical Domains Framework [71] and the Policy Triangle Framework [72].

Reflecting on the findings, a list of practical recommendations (**Table 5.2**) can be suggested, which can be used by policymakers to prevent and mitigate common challenges to successful implementation of medicines policies.

Table 5.2 List of key recommendations for effective medicine policy implementation

➢ Integration of updated evidence-based research
➢ Dissemination of guidelines and SOPs
➢ Ensure financial and human resources by developing an action plan and budget, considering feasibility based on local resources
➢ Inform and create awareness among all staff
➢ Provide training on implementation, communication skills and team management
➢ Consider ways to provide some form of professional recognition for staff (such as incentives and rewards)
➢ Ensure effective leadership and coordination
➢ Involve staff in the policymaking process
➢ Integrate audits to monitor implementation
➢ Support and disseminate a culture that promotes system changes, professionalism and team work

SOPs Standard Operating Procedures

As for the implementation of HMs policies, given their regulatory differences in different countries and challenges in proving efficacy standards, it seems likely that HMs regulatory implementation experiences would be more complex and require more effort than those of conventional medicines. Since this review lacked papers that investigate specific HMs implementation experiences, in order to adequately inform an implementation of a robust HM registration system, a practical investigation of a well-established system that imports HMs is essential. Such knowledge would provide countries with unsophisticated HMs systems (such as Kuwait) with a strategy on how to conduct an effective implementation.

This review is to our knowledge, the first medicine policy implementation review conducted in the context of a DRA. It is thorough, as a rigorously pre-defined search strategy was followed, a framework that categorises the findings was adopted, and methodological assessment of included papers was undertaken. However, the review has a number of limitations. First, the review was limited to English language published peer-reviewed journal articles found through sources described earlier. There may be other papers published in other languages, particularly as policy implementation is commonly handled locally. Second, there is a lack of studies in HICs, and therefore the review was mostly limited to the experiences in LMICs. Third, there is a diversity of cultural and political contexts across the investigated countries, which made it especially difficult to draw valid specifics, which meant that only general aspects could be highlighted. Fourth, included papers had several methodological deficiencies, however, the assessment of papers facilitated recommendations to further improve policy implementation research.

5.5 Conclusions

This review revealed a dearth of papers that examined factors affecting implementation of medicines regulatory policies within a DRA setting. Although the included papers revealed a number of factors influencing policy implementation, there is still a need for high quality, clear, context specific and relevant research to better understand the underlying causes behind factors associated with medicines policies. More empirical work on implementation, and specifically policy change experiences driven both by relevant theory and rigorous synthesis is required. As for HMs specifically, a practical investigation of a HM classification system of an established system that imports HMs is essential. Such knowledge would also provide a novel and useful contribution to literature, to furnish countries with adequate information for informing HMs registration system for imported HMs. Nevertheless, this paper provided general lessons in planning for future implementation which countries can consider.

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Additional File 5.1

Table 5.1 Data extracted from included papers for analysis of factors affecting medicine policy implementation, and description of papers' focus and methodological rigor

Item	Methods	Population	Results: Facilitators	Results: Barriers	Type of results
(1) Durrheim et al. (2003) **Study design** Case study "comparing specific policy in two areas within one country" "policy change"	**Data collection** Interviews, focus groups participatory exercises and archival documents (qualitative mixed) [triangulation of methods] **Data analysis** Grounded theory **Framework/theory/model** Wilt and Gilson (1994) policy analysis triangle **Study aim** Clear "to explore the policy change from chloroquine to sulphadoxine-pyrimethamine for first-line treatment of malaria in two South African provinces, Mpumalanga and Limpopo Province from the perspective of national and provincial policy"	**Sample population** Policymakers and programme managers (justified) **Sample size** 15 (approach identified) **Setting** South Africa **Discipline** Conventional medicines policy [Malaria treatment policy]	**Political determinants:** Convincing senior government officials for the need to change the policy **Resources determinants:** Training on the change in policy was conducted for all health workers prior to implementation of the change. With the change, the programme manager and his team ensured that all staff were adequately trained Ongoing supportive on-site monitoring Involving malaria researchers in the policymaking **Actors' determinants:** Staff influencing policymakers by presenting the consequences of inaction and convincing them of the negative consequences of not changing the policy (that there would be unnecessary deaths and many more hospital admissions with increased expenditure) Policymakers morality to change the policy in order to prevent unnecessary deaths Gate- keeping power to change policy in the hand of individual senior officials "leadership", which also supported the change from the beginning	**Political determinants:** Lack political influence: large gap between research findings and the utilisation of these findings in policy and practice. A major hindrance to using research-based findings for informing policy decisions was the recognised lack of political influence of the research community. Lack of national sanctioning of proposed changes in policy (need for official endorsement) Publishing the policy change without ratification and approval at national- level;, only in provisional level creating resistance and ultimately slowed implementation of the change **Resources determinants:** Neglecting setting aside specific fund for introduction of the policy nationally for purchasing consumables during first year of implementation Lack of training Failure to use 'lessons learned' from another policy **Cultural determinants:** Disrespectable manners towards lower level staff	**Type of results** Analytical **Notes:** Investigated a comprehensive and informative policy change using a policy analysis model and providing a historical overview of the policy change and factors affecting policy implementation

			Personalising the information – the information on negative outcomes (e.g. increasing hospital admissions); having a personal connection to the area where the death occurred performed impact on policymakers who felt sympathy – taking it personally, which prompted policymakers to improve the policy The influence of previous personal and professional experiences of implementers influenced an effective policy implementation Informing the staff and pharmaceutical suppliers of the exact date of implementation so that timely orders for the new policy could be placed. Thus ensuring that adequate products was available at the provincial depot and ensuring that there will not be drug shortages in the market		
(2) Ferrario, Sautenkova et al. (2014) **Study design** Case study "one nonspecific policy in same country" "current policy "	**Data collection** Field work, review of policy documents and analysis on secondary data (qualitative mixed) **Data analysis** Not stated **Framework/theory/model** WHO data collection tool for the assessment of regulatory systems (2007) **Study aim**	**Sample population** Managers and staff members involved in pharmaceutical regulations in the drug regulatory authority (not justified) **Sample size** 22 (approach not identified) **Setting** Republic of Moldova **Discipline** Conventional medicines policy [medicines registration, procurement	Not stated	**Resources determinants:** Lack of transparency in the regulation of medicines due to low access to information on regulations and procedures for holders of marketing authorisation and lack of standard operating procedures Low human resources capacity for implementation due to low salaries and general paucity of skilled professionals in the country Lack of sufficient funding to conduct its activities and to invest in continuous training of its staff (particularly inspectors and reviewers) Objectivity of decisions taken by officials (reviewers) is weakened due to lack of approved written procedures on how to assess registration applications Lack of time needed to introduce the necessary legislative changes	**Type of results** Analytical **Notes:** Mostly described the current policies and how the system functions, and then focused only on barriers to effectively implement current policies by observing the current implementation process, analysis of current guidelines and published literature

	Clear "to provide an in-depth analysis of the existing pharmaceutical regulation, including recent changes in the Republic of Moldova"	and access] "description of current pharmaceutical policies and analysis to determine whether or not a regulation is effectively implemented and the barriers to its implementation"		**Actors' determinants:** Frequent change of power leading to lack of long-term strategy and plans	
(3) Goodman et al. (2007) **Study design** Case study "one specific policy in one country" "current policy"	**Data collection** Interviews and survey (qualitative and quantitative) **Data analysis** Not stated **Framework/theory/model** None **Study aim** Clear "to explore challenges involved in drug store regulation through a case study of malaria treatment in rural Tanzania"	**Sample population** Sellers from drug stores and officials from the drug regulatory authority involved in the policy (justified) **Sample size** 30 for interviews 30 for surveys (approach indented) **Setting** Tanzania **Discipline** Conventional medicine policy [malaria treatment policy in drug stores]	Not stated	**Political determinants:** Lack of sanctions and successful concealment of regulatory violations **Resources determinants:** Severe constraints in regulatory implementation due to insufficient manpower and transport Lack of inspections **Actors' determinants:** Poor knowledge of implementers on how to implement the regulation as a result of outdated regulation **Cultural determinants:** Tacit permission of inspectors (drug inspectors aware of regulatory violations, but still allowed violators to continue). This is as a result of lack of knowledge and willingness to improve Relationships between inspectors and workers at the pharmacy also affect the decision inspectors take	**Type of results** Descriptive **Notes:** Only focused on the challenges in implementing the policy
(4) Hlongwana and Tsoka-	**Data collection** Interviews (qualitative)	**Sample population** Researchers (knowledge producers), policy makers	**Political determinants:**	**Resources determinants:**	**Type of results** Descriptive

Gwegweni (2017) **Study design** Not stated "one specific policy in one country" "policy change"	**Data analysis** Thematic analysis **Framework/theory/model** None **Study aim** Clear "to investigate the stakeholders' understanding of the malaria elimination policy in South Africa, including their perceived barriers and facilitators to policy implementation"	and policy implementers staff (justified) **Sample size** 12 (approach identified) **Setting** South Africa **Discipline** Conventional medicines policy [malaria elimination policy]	The political pressure of international organisations such as the World Health Organisation and neighbouring countries to see the policy through to implementation Management of cross-border migration Cross-border collaborations with neighbouring countries The development and implementation of malaria elimination policy as a response to a global political mandate/pressure	Lack of adequately trained workers Poor capacity Lack of financial resources Lack of effective intervention tools Closure of the Malaria Research Unit (through organisational restructuring) of the South African Medical Research Council (MRC), which was responsible for managing the country's malaria information systems, negatively affected the implementation of the malaria elimination strategy **Actors' determinants:** Staff attitudes Lack of intra and interdepartmental collaboration **Cultural determinants:** Lack of interest in improvement	**Notes:** Mostly perceptions about the impact of the policy and why is it important Discussed only few factors affecting policy implementation
(5) Klika et al. (2017) **Study design** Case study "comparing one policy in different countries" "current policy"	**Data collection** Interviews (qualitative) **Data analysis** Not stated **Framework/theory/model** None **Study aim** Clear	**Sample population** Participants from national regulatory authorities, and healthcare professionals (not justified) **Sample size** 33 (approach not identified) **Setting** Germany, Poland, Portugal, France, Finland and the United Kingdom	Not stated	**Political determinants:** Strict data protection law and strict access to information by other organisations (health insurance) **Resources determinants:** Economic crisis and scarcity of resources Lack of time and skills, awareness campaigns, mandatory courses on the policy, advanced post-graduate training Low awareness levels in patients to report due to lack in awareness-raising campaigns to increase public knowledge about reporting of side effects because of low resources dedicated to awareness-raising **Actors' determinants:**	**Type of results** Descriptive **Notes:** Mostly described and compared how the current system works (the content) in different countries and the impact of the policy from perceptions of implementers with little insights into challenges in implementation

	"to present a critical assessment of the current adverse drug reaction reporting in the European Union and its Member States. It examines the latest pharmacovigilance reform, identifying serious challenges of practical implementation at the national level"	**Discipline** Non-specific medicine policy [pharmacovigilance system]		Lack of cooperation between relevant actors **Cultural determinants:** Perception of adverse drug reaction being a sign of failures and the perceived loss of reputation between healthcare professionals	
(6) Modisenyane et al. (2017) **Study design** Case study "one specific policy in one country" "policy change"	**Data collection** Interviews, systematic review of documents and review of policy documents (qualitative mixed) **Data analysis** Content analysis **Framework/theory/model** None **Study aim** Clear "to explore state and non-state actors' perceptions regarding how domestic health policy is integrated into foreign policy. The ultimate goal of this study was to achieve better insights into the health and foreign policy processes at the national level"	**Sample population** Participants from drug regulatory authority, non-government organisation, academia and think tanks (justified) **Sample size** 21 (approach identified) **Setting** South Africa **Discipline** Conventional medicine policy [access to antiviral medicines]	**Political determinants:** Political powers were invited to chair numerous technical and advisory committees	**Political determinants:** Power struggle between different levels of the government **Resources determinants:** Slow development of programme infrastructure Lack of global experience Lack in a formal coordinating structure or permanent secretariat to manage the implementation	**Type of results** Descriptive **Notes:** Very difficult to extract information as the results were written as stories and not categorised. Limited results; did not explain why such factors exist

(7) Powell et al. (2010) **Study design** Not stated "comparing one specific policy in different countries" "current policy"	**Data collection** Workshops (focus group method) (qualitative) **Data analysis** Not stated **Framework/theory/model** None **Study aim** Not clear	**Sample population** Senior pharmacists, drug regulatory authority officials, Ministry of Health personal, senior physicians and nurses (not justified) **Sample size** Not clear (approach not identified) **Setting** Ethiopia, Kenya, Malawi, Rwanda, Tanzania and Zambia **Discipline** Conventional medicines policy [Opioids access regulation]	Not stated	**Political determinants:** Complex bureaucratic procedures with central government, which render policy change a protracted process Restrictive legislation (does not take into consideration certain circumstances, which makes it very difficult to be implemented as it it) **Resources determinants:** Inadequate funding to ensure effective implementation and sustainability Lack of technical assistance to develop medical training curricula Lack of strategic plans and budgets Absence of guidelines for implemented workers **Actors' determinants:** Lack of dedicated leadership Misplaced negative attitudes of implementers **Cultural determinants:** Culture of blaming, fear and punishment Lack of knowledge and interest in improving	**Type of results** Descriptive **Notes:** The objectives of this paper was not clear, and the findings concentrated only on perceptions of challenges in implementing the policy
(8) Rawson et al. (1998) **Study design** Not stated	**Data collection** Telephone interview and survey (qualitative and quantitative) **Data analysis** Not stated	**Sample population** Healthcare professionals in clinics that approved (Levo-alpha-acetylmethadol) (not justified) **Sample size**	Not stated	**Political determinants:** Extensive and time-consuming policy approval process **Resources determinants:** Lack of administrative procedures to follow the policy Lack of training	**Type of results** Descriptive **Notes:** Presented more about the perceptions of implementers towards

"one specific policy in one country" "policy change"	**Framework/theory/model** None **Study aim** Clear "to describe the course of Levo-alpha-acetylmethadol's implementation and to document some of the factors that have influenced the time course and extent of this process"	Not stated **Setting** United States **Discipline** Conventional medicine policy [Levo-alpha-acetylmethadol registration for maintance treatment of opioid dependence]			the impact of the policy than implementation challenges, the aim did not match the findings
(9) Sheikh and Uplekar (2016) **Study design** Case study "comparing one specific policy in different countries" "policy change"	**Data collection** Interviews and document review (qualitative mixed) **Data analysis** Thematic analysis **Framework/theory/model** "action centred" framework adapted from Ratanawijitrrasin and Wondemagegnehu: regulatory processes can be seen as involving interactions between groups of actors within social and organisational contexts, and at different levels of policy and implementation. This approach seeks to understand regulatory processes through the lens of the experiences and perspectives of	**Sample population** Policy and health system actors (justified) **Sample size** 89 (approach identified) **Setting** India, Tanzania and Zambia **Discipline** Conventional medicine policy [regulation of Tuberculosis]	**Political determinants:** Tanzania: political support (government with other countries that exports Tuberculosis medication **Resources determinants:** Tanzania: regular supervision and monitoring visits India: stringent monitoring for the implementation **Actors' determinants:** Tanzania: adherence to guidelines	**Resources determinants:** Zambia: limited financial resources to import the medicine Zambia: mismanaged implementation (no plan) India: lack of inspection and monitoring **Actors' determinants:** Zambia: Non- adherence to the guideline by implementers India: Non- adherence by pharmaceutical companies **Cultural determinants:** The perception that the system does not need improvement as long as it works	**Type of results** Analytical **Notes:** Mainly the findings concentrated on the historical process of approving the policy than on factors influencing it and reasons behind these factors

	these policy and health system actors, which is achieved by conducting qualitative research to access these experiences **Study aim** Clear "to elaborate processes of regulation of quality and availability of Tuberculosis medicines in three Low and Middle Income Countries – India, Tanzania, and Zambia – and to understand the factors that constrain and enable these processes"				
(10) Suleman et al. (2016) **Study design** Not stated "comparing one policy in different countries" "current policy"	**Data collection** Interviews, archival review, cross-sectional survey (qualitative and quantitative) **Data analysis** Descriptive analysis **Framework/theory/model** None **Study aim** Clear	**Sample population** Key informants involved in the pharmaceutical sector of academia, industry and regulatory system (justified) **Sample size** 12 for interviews 249 for surveys (clear approach) **Setting** Ethiopia, South Africa, Tanzania and Uganda, European Union	**Political determinants:** Strong political commitment from government to support the pharmaceutical sector in general and the regulatory system in particular. The government empowered the regulatory authority to hire staff and acquire resources	**Political determinants:** Lack of regulatory tools; regulations are not enforced by a law Weak regulatory enforcement, poor inter-agency cooperation between law enforcing bodies and weak border control (Pharmaceutical products smuggling due to weak costumes control. These smuggled products are sold in unregulated markets, retail outlets and even licensed clinics) Decentralisation of the regulatory activities to lower-level administrations with weak control capabilities creating regulatory gaps and contributed to smuggling **Resources determinants:**	**Type of results** Descriptive **Notes:** Majority of findings focused on comparing the content of the policy in different countries and focused on implementation challenges in one country

	"to assess the pharmaceutical regulatory system in Ethiopia and to reveal possible reasons for deficiencies in the pharmaceutical chain"	**Discipline** Conventional medicine policy [medicine registration, procurement and access]		Lack of established system with clearly identified roles and responsibilities of parties involved including standard operating procedures Significant shortage of qualified and skilled human resource, due to law salary and lack of attractive career structure No adequate financing to perform routine regulatory activities due to insufficient government funding and weak revenue generating system **Actors' determinants:** Weak cooperation between the authority and the prosecutors at court, therefore most illegal cases taken to court were not successful **Cultural determinants:** Inspections not perceived as duties	
(11) Williams et al. (2004) **Study design** Case study "comparing specific policy in different countries" "policy change"	**Data collection** Interviews, focus groups and review of historical documents describing policy process (qualitative mixed) **Data analysis** Not stated **Framework/theory/model** None **Study aim**	**Sample population** Key informants involved in the policymaking process (justified) **Sample size** Not stated **Setting** Malawi, Tanzania, South Africa, Kenya and Peru **Discipline** Conventional medicine	**Political determinants:** Utilising regional approaches, rather than focusing solely on the home country (to understand how other countries in their particular geographical regions were addressing similar problems, by reviewing drug efficacy data from neighbouring countries) **Resources determinants:** Using rigorous evidence (providing data from real world experiences for policy change from sectors expedited changes, thinking about compliance and community responses) Including scientists as part of the decision making team rather than only as contributors of research findings	**Political determinants:** Political changes affecting government stability (re-organisation of the Ministry of Health resulting in 50% of technical staff were lost) Competition from other and, at times, more pressing national priorities (policy makers focusing on other policies, shifting attention away from other equally important public health problems) Defensive posture of Ministries of Health when interacting with the media (little attention had been paid to the potential power and influence of the media. This resulted in defensive responses countering allegations about lack of action) **Resources determinants:** Lack of standardised data on drug resistance	**Type of results** Descriptive **Notes:** Provided rich experiences from different countries with incorporating the context and therefore explaining the reasons behind the existence of the certain factors

	Clear "identifying and understanding the key influences that affect decision-making, and factors that facilitate or undermine policy implementation"	policy [malaria treatment policy]	International support (Discussing the data in forums that included international partners (technical experts or World Health Organisation) enhanced the credibility of the national scientists and control staff, and was seen as a positive step in gaining support from other stakeholders. **Actors' determinants:** Focusing communication on problem solving, rather than confrontation Involving programme staff as members of research team. This process provided actors with additional skills and understanding	Inadequate resources, both financial and human **Actors' determinants:** Poor communication between key stakeholders (especially researchers and Ministry of Health officials responsible for the policymaking process; officials distrusted any data generated without their input, and manifested different priorities and agenda) **Cultural determinants:** Lack of knowledge and interest in quality improvement Inspections perceived as way of controlling staff	

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6. Chapter Six: Study Three and Four

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A Qualitative Exploration of Bahrain and Kuwait Herbal Medicine Registration Systems: Policy Implementation and Readiness to Change

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Abstract

Background

The Kuwaiti drug regulatory authority (DRA) lack a structured classification system for the assessment of imported herbal medicines (HMs), which leads to ambiguity in the registration process. This study aimed to examine the policy development and implementation process in an established HM registration system (Bahrain) and harness lessons to inform recommendations for a suitable HM classification system and explore implementation readiness in Kuwait.

Methods

A sequential study design was chosen, with data collected in Bahrain (case 1), recommendations formed and readiness for implementation explored subsequently in Kuwait (case 2). With ethics and DRA approval in place, data sources were documentary review of regulatory policies, direct observations of HMs registration processes, and semi-structured interviews with twenty three key officials involved in the HMs registration processes. Data from all three sources were analysed thematically and findings triangulated.

Results

The classification policy in Bahrain was found to be based on evidence and extensive stakeholder engagement, resulting in a clear and organised HM registration process. The availability of HMs classification policies in other DRAs, officials' dedication and teamwork, and support by higher authority, were identified as the main facilitators in policy development and successful implementation. Barriers were the diversity of HM classifications worldwide, a lack of staff and resultant workload, and lack of training. Proposed recommendations for Kuwait were to adopt a clear definition of what constituted HMs, and to introduce a Traditional Herbal Registration based on this definition and the product's characteristics. Interviews in Kuwait showed that almost all participants were in favour of the proposed recommendations and were in support of timely implementation. Interviewees anticipated that consistency in the HM registration process would be the main benefit, increasing reviewer's confidence in making regulatory decisions. Interviewees also identified potential challenges which may impede successful implementation, including staff shortages, resistance to change by internal and external stakeholders, and the impact of cultural and traditional ways of working.

Conclusions

Insights into the HM policy development and implementation process in Bahrain, and exploration of Kuwait's readiness to implement resultant recommendations informed an effective implementation process for a well-designed HMs policy for Kuwait and other Arab countries.

6.1 Background

Herbal medicines (HMs) have been gaining increased popularity among consumers in both developed and developing countries. According to the World Health Organisation (WHO), 60% of the world's population, and 80% of the population in developing countries depends on HMs for their healthcare needs [1]. Global consumption of HMs has grown significantly from $20 billion in 1997 to $83 billion in 2008 [2]. Whilst a range of definitions exist for HMs, in this study, HMs are defined as ''herbal preparations that are manufactured industrially in which the active ingredient(s) is/are purely and naturally original plant substance(s), which is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product'' [3].

The public commonly perceive HMs as safe [4], yet there are concerns about their safety too. Several adverse effects, some of them life threatening, can arise from active ingredients themselves, as well as adulteration of HMs with conventional medicines, herbal-drug interactions and inappropriate HMs formulations [5-10]. However, significant HM safety issues also arise mainly from the inappropriate regulatory classification of HMs [11, 12]. For example, in the United States (US), HMs are classified as dietary supplements, with requirements for evaluating quality and safety less stringent than those for medicinal products. This means that these products do not require assessment by the national drug regulatory authority (DRA) prior to their marketing [3, 4]. This has particular implications for many countries in the Eastern Mediterranean Region (EMR), which import the majority of their HMs from other countries including the US [13]. For a pharmaceutical manufacturing company to import and distribute HMs in these countries, it must appoint local agents, who act on behalf of the pharmaceutical company in communication with the responsible DRA to facilitate the submission of all documentation and materials for marketing the product.

Kuwait is a country that does not manufacture but imports all HMs from other countries, a HM classification system is lacking and there is no clear definition of what constitutes a HM in its DRA structure. The submission of documentation and regulatory control imposed depends mainly on how these products are classified in the country of origin [14]. This means that many HMs may escape rigorous assessment as they are marketed as dietary supplements in their country of origin. Clear classification

and definition of imported HMs in the Kuwaiti DRA structure is therefore essential, in order to determine the level of regulatory control that would guide the product into the most appropriate and consistent conformity assessment for evaluating quality, safety and efficacy.

An important parameter to inform policy redesign for imported HMs in the Kuwaiti DRA structure is to explore DRAs' approaches to HM regulations in more established systems. Therefore in 2018, a comparison of regulatory processes in five such countries was performed to investigate their existing HMs definition and classification policies. These countries were; the United Kingdom (UK), Germany, US, United Arab Emirates and Bahrain. This country comparison found a lack of consistency in the definition of what constitutes an HM, and how these are assessed and regulated. The study however recommended a universal definition for HM registration for Kuwait and other EMR countries that do not have such laws implemented [3]. The study also provided with an international HM classification option called the Traditional Herbal Registration (THR), where instead of a full registration as a conventional medicine (i.e. requiring a marketing authorisation and proven clinical efficacy), 'plausible efficacy' due to established history of traditional use is sufficient to assure efficacy, and evidence of bibliographic data or toxicological tests is sufficient to assure safety [3].

Nevertheless, a study of policymaking must also be concerned with an investigation of its implementation and whether implementers comply with it [15]. Therefore, relevant literature on implementation of medicines regulations including herbals was reviewed and it was recommended that more empirical work on policy implementation, driven both by relevant theory and rigorous synthesis is required [16-19]. Moreover, despite the WHO international guidelines, reports and consensus on HMs [20- 26], countries still experience complications in the implementation of HM regulations, due to their diversity [27]. Analysing previous polices in similar political and cultural context can provide reliable facts and knowledge on how policies were developed and implemented, and ensures that recommendations are supported and resourced with the best available evidence and research [28]. Therefore, insights into a HM registration of an established system of a country that is similar to Kuwait is essential. However, if proposed recommendations are to be implemented in Kuwait, some change will occur. Being ready for this change is important for successful implementation. Smith indicated that there is high risk of implementation failure if

organisational or individual readiness for change is low [29]. Therefore, the best approach is an investigation of an organisation's readiness for overall change before any implementation attempt in Kuwait; such an investigation can reveal factors about the potential success of the intended policy [29]. There are numerous studies available in the literature that describe existing frameworks to guide how readiness for change can be assessed [30- 32].

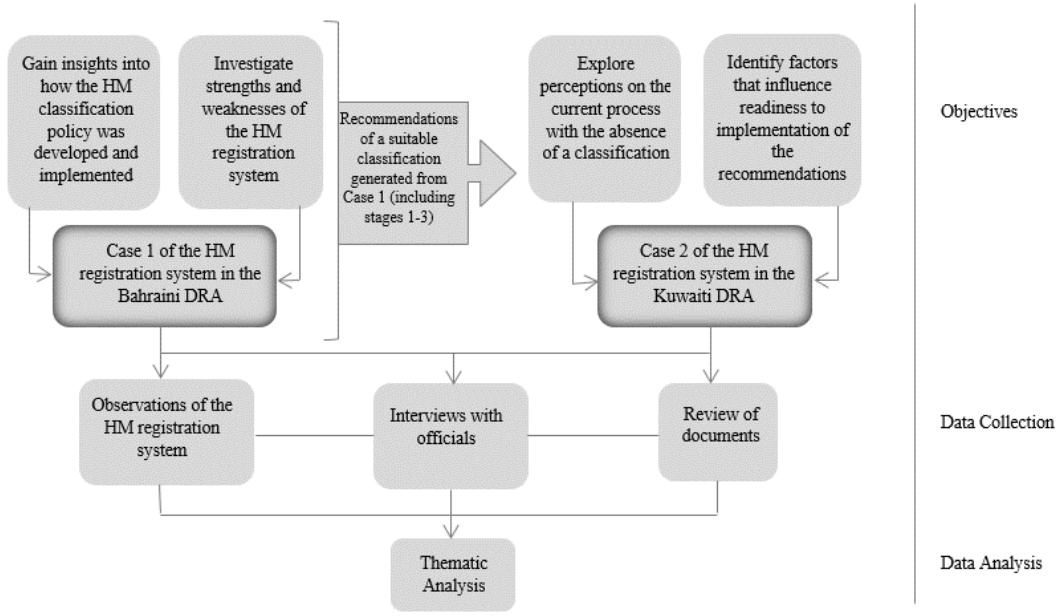
The aim of this study was to examine policy development and implementation process in an established HM registration system (Bahrain) and harness lessons to inform recommendations of a suitable HM classification system in a less developed DRA (Kuwait), and explore implementation readiness there.

6.2 Methods

6.2.1 Study design

The last decade of policy implementation science witnessed great interest in the use of theories and frameworks to gain insights into policy implementation and understand system strengths and weaknesses [33- 35]. In this study, the conceptual model for policymaking by Anderson [15] was adopted, which consists of five steps. The first two steps have been addressed in the introduction: (1) the problem being the absence of a classification and definition for imported HM registration in the Kuwaiti DRA structure, and (2) the formulation of options for HM classifications and a definition of what constitutes a HM through a comparative study of five advance systems [3]. For steps (3) (stating content) and (4) (implementation) of the policy process, this study employed a qualitative research design in two countries (cases): case 1: an established HM system (Bahrain) and case 2: Kuwait (**Figure 6.1**).

Figure 6.1 Summary of the objectives, data collection methods and data analysis carried in case 1 and case 2



DRA drug regulatory authority, *HM* herbal medicine

Case 1 focused on performing policy analysis of the HM classification policy in the Bahraini DRA using the policy triangle framework by Walt and Gilson [36], and investigated the system strengths and weaknesses to formulate recommendations for Kuwait. The DRA in Bahrain was chosen due to its geographic proximity, common culture, shared faith, and its economic and political alliance with Kuwait through the Gulf Cooperation Council (GCC). Most importantly, Bahrain is similar to Kuwait in that it imports all of its HMs from other countries through local agents. In 2016, the Bahraini DRA introduced the Pharmaceutical Product Classification (PPC) policy which clearly defines and classifies HMs [37].

Investigating the strengths and weaknesses of an established system is found useful for informing policies in unsophisticated systems [34]. Walt and Gilson explained that when researching health policy not only policy content, but also actors, context and processes need to be investigated. In this study, the four elements were used as a framework to investigate and structure data about; the policy context within which the policy was developed (i.e. context for and reasons why the policy was developed); the policy process (i.e. how the policy was developed and is being implemented); the policy content (i.e. how the content was formulated); and the actors involved (i.e. who were they and what role they played in the process). The framework

has influenced the research of health policy in many countries, and has been used to analyse numerous health issues [38, 39].

Case 2 focused on identifying the current weaknesses of the system in Kuwait and readiness of staff in the Kuwaiti DRA to implement recommendations informed following case 2. Based on the Theory of Organisational Readiness for Change (TORC), Weiner [31] proposed a set of factors that the organisational members can take into consideration to formulate their change ability judgements. This study did not use the full theory process, but adopted five contextual factors from TORC which thought best achieve the aim of the study. The factors were used as a framework to structure insights into (i) policies and procedures that might influence how the recommendation could be implemented, (ii) past experiences of previously implemented policies, (iii) organisational resources that could influence readiness for implementation, (iv) organisational culture and how individuals behave towards the change, and (v) whether the change will influence the infrastructure of the organisation.

For both cases, data collection involved direct observation, documentary analysis and semi-structured interviews (**Figure 6.1**), all undertaken by the first author who had undergone appropriate training.

6.2.1.1 Study participants

Approval was obtained from senior management working in the registration of HMs in Bahrain and Kuwait DRAs, who identified all senior and middle managers and all scientific reviewers who worked directly with the registration of HMs. Managers are the decision-makers of policies affecting the registration of HMs and scientific reviewers are employees who implement the HM classification policy and carry out the scientific assessment and quality control analysis for HMs. Identified participants were approached by the interviewer/observer during the visit in each authority and given a study information sheet. Managers were asked to participate in interviews, and scientific reviewers were asked to participate in observations and interviews, and if they agreed, an appointment was set.

6.2.2 Data collection

Data collection in case 1 and 2 targeted HMs in the DRAs' departments with criteria specified in (**Table 6.1**) which are based on the current characteristics of HMs

registered at the Herbal Department in the Kuwaiti DRA. Herbal teas and coffees were excluded although being one of the registered products at the Herbal Department, as these products have separate and clear definition and registration requirements as per Ministerial Decree 201/99. In Bahrain (case 1) data were collected between October-November 2017, and in Kuwait (case 2) between (April-May 2018).

Table 6.1 Data collection inclusion and exclusion criteria for HMs in Bahrain and Kuwait drug regulatory authorities

Inclusion criteria	Exclusion criteria
Herbal preparations that are manufactured industrially consist of active ingredient(s) that is/are purely and naturally original plant substance(s), is/are not chemically altered and is/are responsible for the overall therapeutic effect of the product	Other types of preparations including homeopathic products, cosmetics, medical devices and medicines containing herbal substance(s) as active substance(s) that has/have been synthesised or chemically altered Raw herbs that are not manufactured industrially HMs as teas or coffees
HMs used for curing purposes or supporting body functions	HMs that do not have a therapeutic effect or are used as flavours or additives or have a cosmetic effect
HMs for human use	HMs for animal use
HMs registration for the consumption of the general public	HMs that are not supplied for the consumption of the general public but for the purpose of supplying to specific individuals by healthcare practitioners following a one-to-one consultation
Premarketing registration of HMs (initial registration)	Post-marketing surveillance of HMs

HMs herbal medicines

6.2.2.1 Observations and documents

Data collection in each case began with non-participant observation of the HM registration process, by chronologically following the scientific reviewers' registration process from initial request for product registration until product authorisation for marketing. The actual HMs observed remained anonymous, and it was not feasible to observe a specific product as the approval process can take months or years. Ongoing verbal consent was obtained at the start of each observation, which could involve the same or different scientific reviewers.

Detailed fieldnotes were taken during three main areas of the registration process of HMs, namely, the regulatory review processes milestones (i.e. types of activities and description of tasks), regulatory requirements and estimated timelines for key milestones of the review process. Because neither authorities have legislated

timelines, in each stage, observed scientific reviewers were asked to provide the minimum and the maximum number of days it took them to complete each activity from an electronic document that records the start and end date of each activity (i.e. date of submission, date of review, date of registration, etc.). Throughout observations, the researcher asked participants some clarifying questions. Regulatory documents relating to the HM registration process such as registration requirements, registration guidelines and ministerial decrees were also analysed.

The main purpose of observations and documents review was to understand the regulatory review practices and the approaches undertaken to classify and register HMs in each authority.

6.2.2.2 Interviews

Face-to-face semi-structured interviews with participants at their place of work followed observations. Signed informed consent was obtained before each interview and to guarantee anonymity, a code was assigned to each participant. Interviews were audio-recorded, with permission, and for interviewees who did not want to be audio-recorded, extensive notes were taken. All interviews were conducted in English, but some responses were made in Arabic.

In case 1, interviews aimed at exploring how the Pharmaceutical Products Classification (PPC) policy in the Bahraini DRA had been formulated and implemented, the strategies and activities used, and the actors involved. Participants were also asked to reflect on their experiences on factors which might have acted as facilitators or barriers, and provide their views on the current system's strengths and weaknesses. The interview guide was informed by a review of the policy science and implementation literature [40- 44].

In case 2, interviews focused on participants' perceptions of the current HM registration system in the Kuwaiti DRA in the absence of a classification and definition for HMs, and their perceptions and readiness for implementing proposed recommendations for a suitable definition and classification procedure for HMs. Interview questions were guided by the five contextual factors from TORC [31].

6.2.3 Data Analysis

All handwritten fieldnotes and audio-recordings were transcribed verbatim using Microsoft Word ^{TM} 2010. Interviews that included Arabic responses were translated

into English by the interviewer who is bilingual in English and Arabic. Each collected document was reviewed and then summarised electronically describing its type, title and purpose. All three data sources were subjected to thematic framework analysis, involving five step process; familiarisation, coding, identifying a thematic framework, charting data into a matrix and interpreting the data [45].

In both cases, all data were thoroughly read for familiarity. Coding was performed by underlining segments of texts that addresses the themes in the observations and interview guide. Development of more codes was performed based on the themes in concepts and theories; for case 1 by Walt and Gilson's policy triangle framework [36] and the strategic environment analysis to identify Strengths, Weaknesses, Opportunities and Threats (SWOT) [46] in the HM registration system, and for case 2 by Weiner's five contextual factors of TORC [31]. Coded data from observations, documents and interviews were summarised in a matrix for each theme comprising of one row per participant or document or observation, and one column per code and inserted into corresponding cells in the matrix using Microsoft Excel ™ 2010. Connections within categories were made and key similarities and differences were identified.

Ethical approval was obtained from the University of Manchester Research Ethics Committee (reference number 2017-1086-3939).

6.3 Results

Findings are presented in two parts; each part represents a case; case 1 being for the Bahraini DRA; National Health Regulatory Authority (NHRA), case 2 from the Kuwaiti DRA; Kuwait Drug and Food Control and Administration (KFDCA). All key officials that work directly with the registration of HMs in Bahrain and Kuwait DRAs participated in the study: eight officials from the Bahraini DRA; five reviewers and three managers, and fifteen officials from the Kuwaiti DRA; nine reviewers and six managers. For description of sources of data used in each case, see Table 6.1 in Additional file 6.1. Summarised data from fieldnotes and documents about the HM registration process are illustrated to show a detailed chronological description and a map of the process in each authority. The timelines in the process are estimations, as not all reviewers keep record of the start and end date of each activity. Quotations from interview transcripts are presented as examples of particular themes or issues.

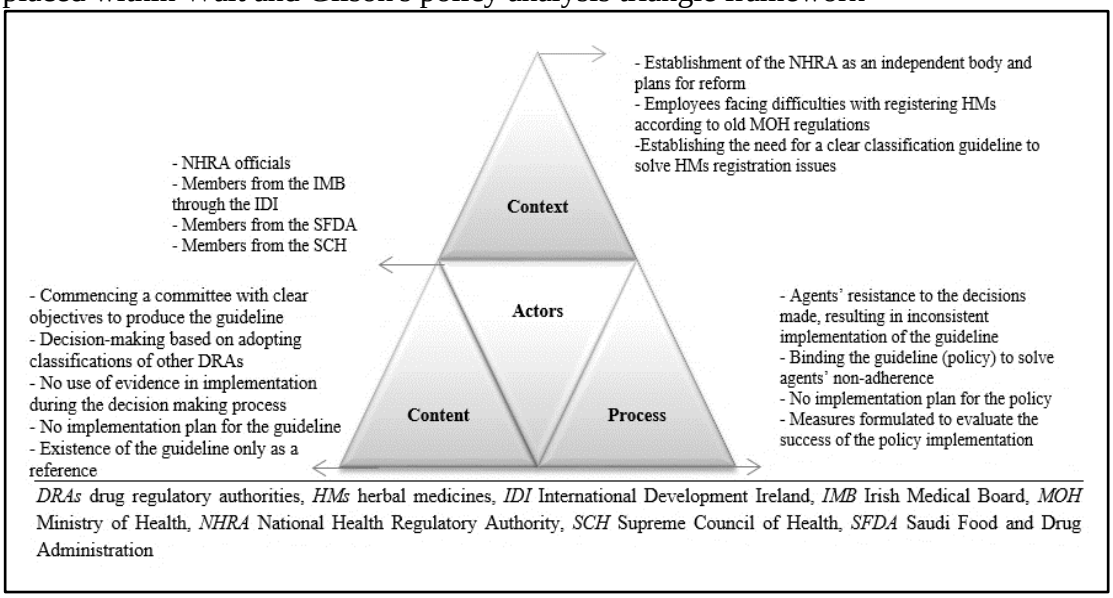
All translated Arabic quotes included in this paper are presented in a table in (Appendix 6.1) to show the original Arabic quote alongside the English translation. As a result of the small number of participants in each case, to maintain anonymity, the official title and positions of managers and reviewers are not mentioned.

6.3.1 Case 1

6.3.1.1 Context, actors, content and process in the development and implementation of the PPC policy in the Bahraini DRA

The triangle in (**Figure 6.2**) presents the results within Walt and Gilson's policy analysis triangle framework. For a clear timeline of the chronological progress of the Pharmaceutical Product Classification (PPC) policy development and implementation, see Figure 6.1 in Additional file 6.2.

Figure 6.2 Case 1 results of the Pharmaceutical Product Classification policy development and implementation process in the Bahraini drug regulatory authority, placed within Walt and Gilson's policy analysis triangle framework



Context

Findings revealed that the development of the PPC policy was triggered by a transfer in the official body of medicines regulation in Bahrain, which coincided with the launch of the 2030 Economic Vision by the King of Bahrain in 2009. The vision aimed at developing Bahrain's economy while focusing on improving the health sector. Emphasis was placed on the need for structural, administrative and financial

independence of the regulation of the entire healthcare system by a DRA from the Ministry of Health (MOH) (Economic Vision 2030). Consequently, Law 38 of 2009 was issued by the King to transfer the regulation of health services including medicines from the MOH to the NHRA.

After the transition was complete in 2011, reviewers were facing issues in registering HMs, as at that time, many submitted HMs were reviewed as conventional medicines as per Law 18 of 1997 which was initially implemented in the MOH. The law was not clear as it did not specify explicit definitions for HMs, and participants described how agents used to submit any HM as a conventional medicine and were then unable to provide all required documents to fulfil HMs registration, which resulted in the refusal of many HMs. As one participant stated:

> *"During transition registering herbals was very hard, no documents for registering herbals was there, we were not really sure what requirements we should ask companies to provide, we were confused, agents were confused" (KI6)*

The development of the PPC policy therefore started with the NHRA management developing a classification guideline to provide clear definitions for medicines and HMs.

Actors

Reviewed documents and interviews revealed that in 2012 the Bahraini government had invited bids to develop policies for the NHRA, following which the Dublin base consultancy International Development Ireland (IDI), was appointed. Having established the need for a classification guideline, the IDI Technical Support Services committee was established, which consisted of experts from the Irish Medical Board (IMB) and the Saudi Food and Drug Authority (SFDA) who had been chosen for their scientific and regulatory expertise in HMs and in developing regulatory guidelines. All managers and scientific reviewers responsible for the registration of pharmaceuticals and HMs in the NHRA were represented. Study participants mentioned that the main reason for including external experts in the development of the guideline was to ensure independent and guard against bias in the development process. The committee was chaired by the NHRA's Chief of Pharmaceutical Product Regulation Department who assigned roles to the members, guided the committee in terms of tasks and process, and set a production deadline of three months.

Content

Guideline production

Findings from interviews revealed that the guideline was developed over a number of steps through regular committee meetings, which are described below. (for more detail and participants' quotes, see Figure 6.1 in Additional file 6.3).

The first step was a) preparing the scope. This involved the identification and analysis of previous MOH regulations with potential relevance to HMs and a comprehensive literature search. An initial scope report detailing which classification matters the guideline should discuss was drafted based on mutual recommendations from all committee members. This report recommended that an existing system that would provide international standards for HMs classification should be adapted.

The second step consisted of b) an online search of classifications in the SFDA, the IMB and authorities that are recognised by the WHO as having competent international recognised and established medicine registration systems. The NHRA investigated the European Medicines Agency (EMA), Health Canada, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the United States Food and Drug Administration (U.S FDA).

The third step was c) the formulation of recommendations. Interviews revealed that the recommendations were drafted using vote counting, and that the majority of the guideline information was *"copied and pasted"* from the SFDA, with some additional detail based on other reviewed DRAs' classifications. When participants described that the reason for adopting the majority of the SFDA's classifications, was that beside the political and cultural similarities between the two countries, the authority was aiming to increase harmonisation of HMs classification in the GCC countries. Such a standardised guideline was seen as facilitating a future GCC central registration system for HMs, which would allow authorisation of a single HM in all GCC member states at the same time.

In the fourth step d) the guideline was finalised in 2013 and signed by the Chief of Pharmaceutical Product Regulation Department and the NHRA Chief Executive Officer (CEO).

Participants stated that in order for the NHRA to remain independent from the MOH, it must comply with the Quality Management System (QMS) standards accredited by the International Organisation for Standardisation (ISO); an

international independent organisation that offers accreditation based on evaluation of the quality, safety and efficiency of systems. According to the QMS standards, all guidelines including the PPC guideline, must be reviewed once every four years.

Guideline implementation

Participants were asked to describe the implementation process, which was defined to them as the actions taken to implement the guideline, and whether an implementation plan such as identifying required resources, training needs and projected implementation issues informed by evidence were developed. Participants confirmed that the committee did not develop an implementation plan. It became clear that the committee did not consider guideline implementation as a process that no training was provided and reviewers simply applied the guideline when registering medicines and HMs. One participant stated:

> *"The implementation was not a process, the guideline was just printed and then we [reviewers] all used it to help us decide what product is a herbal and what product is a medicine" (KI1)*

However, participants revealed that shortly after the production of the guideline, the NHRA introduced the additional service of a classification inquiry which commences before the process of registration. It is available for agents who are uncertain of a product's classification, i.e. whether it is a conventional or a HM. Following an agent's submission of a classification application, this will be assessed by a reviewer, and a committee consisting of members from the Pharmaceutical Product Regulation Department uses factors set in the classification guideline to make its final decision.

Policy process

Policy Production

Initially the guideline had not been binding, and participants described how agents commonly failed to comply with reviewers' classification decisions as they merely viewed them as reference. One of the participants indicated:

> *"The guideline was a reference and not compulsory, sometimes we used it and sometimes we didn't. But agents will not accept what you tell them unless it is some kind of policy" (KI5)*

Therefore, at the beginning of 2016, Decree 9 in relation to Classifying Pharmaceutical Products and Health Products came into force, making the guideline legally binging.

Participants explained that the decree did not repeal Law 18 of 1997, but is to be used in combination to produce more clarity on HMs and their classification. The decree was approved and signed by the Chair of Supreme Council of Health (SCH), which is the responsible body for approving health policies in Bahrain. Members of the SCH were therefore actors in this policy process.

Policy Implementation

All participants confirmed that once again, no implementation plan was developed, nor was training provided to reviewers; implementation consisted of an upload of the guideline on the NHRA's official website, which was also published in Bahrain's official Gazette. Participants stated that management gave reviewers instructions to re-classify registered products according to the new policy while providing an adaptation period for agents to provide required documents.

Policy Evaluation

When asked whether the implementation of the PPC policy was evaluated, participants explained that in order to assess the success of the policy, implementation was evaluated by calculating the total number of successful applications for HMs classified in the medicines registration, health products registration and in the classification committee prior to the legalisation of the guideline in 2015 and after. This confirmed that policy adherence was more effective after binding the guideline to a decree, resulting in a 35 % increase in the registration of medicines, 33% increase in the registration of health products and 576% increase in the number of medicines and health products applications submitted to the classification committee for classification (NHRA annual report 2016).

Facilitators of, and barriers to, the development and implementation of the PPC policy

Having explained the development and implementation process of the policy, interviewees were asked about facilitators and/or barriers they experienced during the development and implementation process, and they identified six general themes. Participants placed much stronger emphasis on facilitators than barriers, which were themed under 'management and collaboration', 'leadership', 'resources', 'nature and content of the policy', 'political and social influences', and 'staff morale and

performance' as described below. For identified facilitators and barriers in the development and implementation phases with participants' quotes, see Table 6.1, 6.2, 6.3 and 6.4 in Additional file 6.4.

Management and collaboration

Many participants identified the facts that the NHRA is trying to build a good reputation of their newly established regulatory body as a facilitator. They further outlined how the collaboration of the NHRA and the IDI had an important role in setting clear objectives and addressing the need to produce effective policies including a classification guideline. Moreover, many participants indicated that the cooperation and teamwork between the NHRA's officials and the external experts from the IMB and the SFDA during committee meetings was conducive for sharing ideas and expertise.

As facilitators in the implementation phase, participants emphasised the importance of effective collaborations with other officials working in the same department, who were enthusiastic, organised and respected. Moreover, reviewers identified regular meetings with the management as important for the discussion of any products that could not be classified using the policy. Decisions that were not based on the classification policy were recorded and taken into consideration when updating the guideline. Some participants also mentioned that the management instruction to set an adaptation period for agents, which allowed the adaptation to the new system, was a strong facilitator of successful policy implementation.

In terms of barriers to implementation, all participants mentioned that the management did not provide a clear policy implementation plan to allocate adequate financial and human resources prior to implementation. According to participants, due to the urgent need in delivering the policy, assessing implementation needs were neglected.

Leadership

Several participants mentioned that the existence of leading figures inside the NHRA facilitated the policy development process. Specifically, participants noted the key role played by the Chief of the Pharmaceutical Product Regulation Department, when leading the production of the classification guideline committee, in terms of planning, organising and meeting the deadline for guideline completion. Moreover, participants

mentioned the leading role of the CEO in approving the guideline and initiating it as a policy, as well as the continuous support and encouragement she offered them.

Strong internal leadership was also identified as an important facilitator in the implementation phase. Participants described effective leadership as having strong figures in the authority who always ensure that staff strictly follow the rules set by the authority.

Resources

All participants identified the availability of funding which allowed the invitation of external experts with the appropriate skillsets as an important facilitator in the development phase. Additionally, as the NHRA deciding to adopt an existing classification system, the online availability of and access to data on HMs classifications and other HMs regulations and guidelines were perceived as important resources, which facilitated the production of the policy. Moreover, participants indicated that the participation of reviewers in the production of the policy facilitated a rapid implementation, as reviewers had a good understanding on how to implement the policy in practice and therefore no training was required.

Regarding barriers, many participants identified the lack in experience and knowledge in HMs, and the lack in decision-making techniques by NHRA members due to lack in training.

Nature and content of the policy

In the implementation phase, all participants indicated that the nature of the policy itself was a strong facilitator of implementation as it contained clear guidance that directs officials and agents on how products should be classified. Participants explained that the policy saved them time, effort and made their job easier. Moreover, some participants mentioned that the facts that the policy had been based on classifications in countries that Bahrain imports from was a key facilitator, as it meant that these products experienced a smoother classification process because of their similarity in regulatory statuses.

Many participants perceived the lack of a universal classification for HMs and the diversity of worldwide herbal regulations as one important barriers in the development phase, creating difficulties for the committee when deciding which classifications to adopt.

As in the development phase, the diversity of classification of HMs worldwide and the continuous change in HMs regulations were also found as challenges in the implementation phase. Participants stated that it was therefore difficult to implement the policy effectively, even when updating the guideline regularly, as complete compliance with the guideline still remained difficult.

Political and social influences

Participants identified the usefulness of previous and current national and international policies in making the case for development of a clear classification policy in Bahrain as clear facilitator in the development phase. For instance, Law 18 of 1997 for the registration of HMs was found to be incoherent and controversial, and was used as a justification to demand action. Additionally, some participants mentioned that Bahrain being a member of the GCC facilitated the production of the policy by adopting another member's classification; Saudi Arabia, and introduced the idea of the policy itself through communications with other members during the GCC central registration meetings. Moreover, many participants identified that gaining structural independence of the NHRA from the MOH was the most important factor that facilitated the production of the classification policy since the approval of policies do not have to go through the lengthy MOH policy process anymore. Finally, strongly linked to leadership, some participants indicated that the existence and the support of the SCH as a across-sectoral organisation responsible for approving all policies produced by the NHRA in an efficient and quick manner was viewed as a significant facilitator to policy development.

As facilitators in the implementation phase, the change in the political climate and the autonomy of the NHRA and its independence from the MOH was once more mentioned by most of the participants, and was seen as an effective factor facilitating the implementation of the policy. Participants explained that after the transition of the regulatory services from the MOH to the NHRA, the MOH could no longer influence the decision-making of applications for products registration. Additionally, many participants identified the binding of the guideline to a decree as facilitating implementation. They explained that the decree illustrates that any violations to its provisions are subject to sanctions outlined in the Law 18 of 1997, and therefore violators would be guilty of an offence punishable by imprisonment and a payment of

a fine. For this reason, agents were found more adherent to the new classification system.

In terms of barriers in the implementation phase, some participants mentioned that they experienced resistance from some agents to comply with the new classifications, particularly before it became legally binding.

Staff morale and performance

As facilitators in the development phase, many participants mentioned that the efficiency of committee officials who participated in the development of the policy and their consistency and commitment in finalising the guideline was a strong facilitator that led to the delivery of the guideline on time.

As facilitators in the implementation phase, similar to the development phase, many participants mentioned staff motivation and dedication as an important facilitator. Participants explained that their motivation in implementing the policy effectively came from them valuing the influence of the regulatory authority in protecting the consumer. They outlined that they have a responsibility to protect the public by complying with the policies of the authority, as they expressed their concern regarding the Arabic culture and the low awareness of consumers using HMs *"like sweets"*, therefore participants believed that by implementing the policy effectively this would safeguard the public.

6.3.1.2 The registration process of HMs in the Bahraini DRA

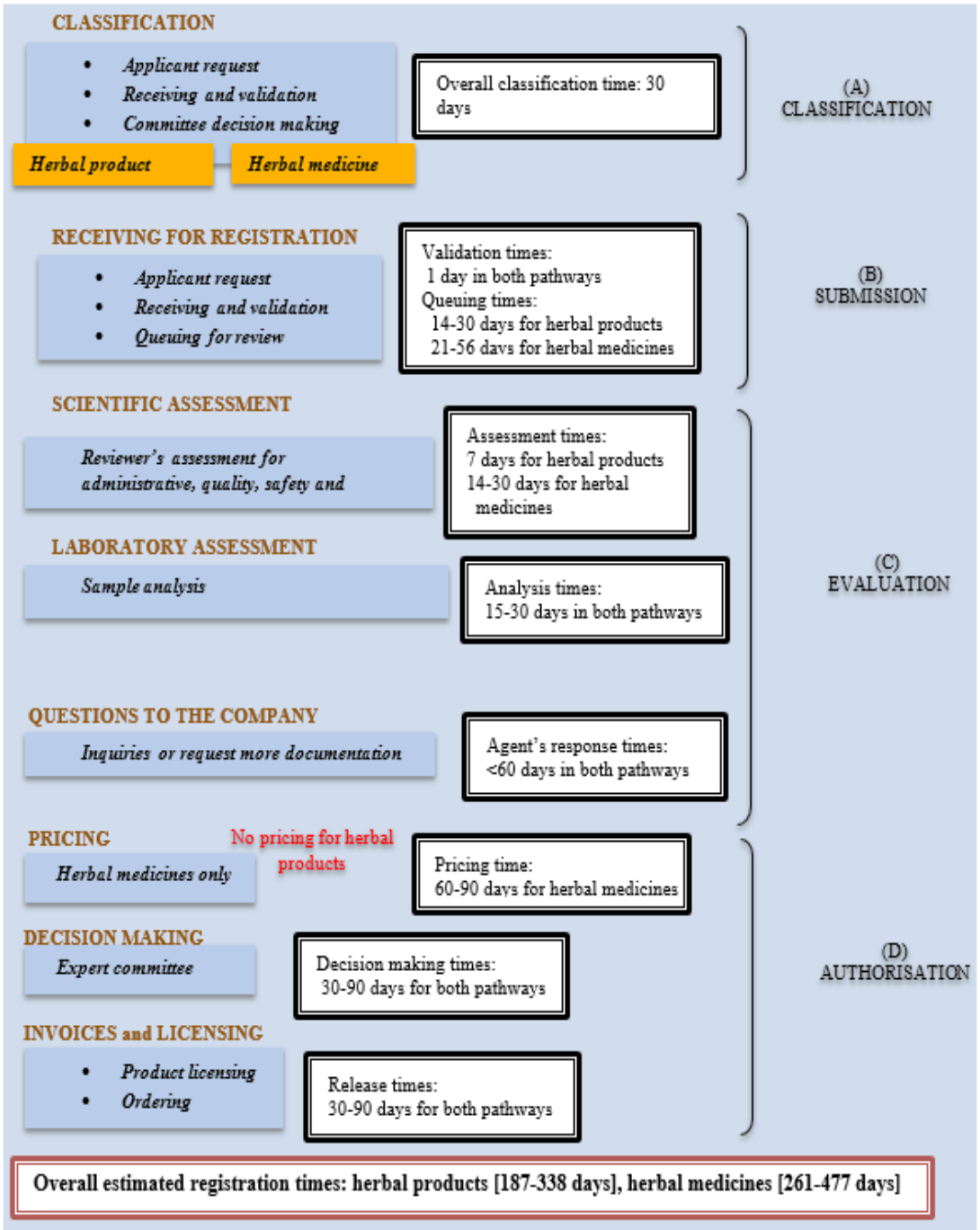
Having discussed the development and implementation processes of the PPC policy, it was essential to investigate how HMs are currently registered and classified in the NHRA after the implementation of the policy. Findings from observations revealed that a HM in the NHRA is classified under two registration pathways, either as a herbal product under the Health Products Registration Department (simplified registration) or as a herbal medicine under the Medicines Registration Department (stringent registration). **Table 6.2** defines HM within each pathway.

Table 6.2 Herbal product and herbal medicine definitions at the Bahraini drug regulatory authority (Pharmaceutical Product Classification guideline)

➢ **Herbal product** "health product containing as active substances, herbal substances or herbal preparations, alone or in combination. It should not carry medicinal indications or make medical claims that are unsuitable for self-diagnosis and self-treatment i.e. without the intervention of a licensed healthcare professional. Any claims made in association with herbal products should be consistent with available evidence regarding the safety and traditional use of those products. A herbal product cannot be sterile, be administered by injection, be subject to a medical prescription, necessitate the intervention of a licensed healthcare professional"
➢ **Herbal medicine** "any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"
In both definitions:
➢ **Herbal substances** are referred to as "whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances"
➢ **Herbal preparation** is "obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates"

From the analysis of fieldnotes and collected estimated timelines of the registration process it was revealed that overall, the regulatory process (**Figure 6.3**) for herbal medicines is more rigorous and therefore takes longer to register than herbal products. For establishing a common ground for comparing the HM regulatory review in both pathways, the processes were divided into A) classification, B) submission, C) evaluation and D) authorisation. For description of the regulatory process including similarities and differences in the process between the two pathways, see Additional file 6.5.

Figure 6.3 Process map of herbal products[a] and herbal medicines[b] registration with estimated times in milestones, extracted from fieldnotes recorded during observations at the Health Products Registration Department and the Medicines Registration Department in the Bahraini drug regulatory authority



a= herbal products: contains claims that are consistent with available evidence of traditional use to demonstrate safety and plausible efficacy, cannot be sterile and/or administered by injection, cannot be subject to a medical prescription and/or requires the intervention of a healthcare practitioner. *b*= herbal medicines: contains explicit claims to treat or prevent a disease that are consistent with available evidence of clinical trials to demonstrate safety and efficacy, can be sterile and/ or administered by injection, can be subject to medical prescription and/or requires the intervention of a healthcare practitioner

6.3.1.3 SWOT analysis for the HM registration system in the Bahraini DRA

A SWOT analysis was conducted based on interview responses. For participants' quotes with identified SWOT, see Table 6.1 in Additional file 6.6.

The most commonly identified strengths were the motivation of the NHRA to continuously improve and amend the system, the clarity and transparency of the review procedure which established set of rules, and the existence of a scientific committee which makes decisions whereby hidden biases are overcome and inappropriate decisions limited. Some participants also identified the availability of clear guidelines and Standard Operating Procedures (SOPs) that assist the pharmaceutical industry and professionals in their compliance as a strength. The use of an electronic system for the review procedure was seen as a further strength, as this limits making errors, misplacing files and missing data.

The most commonly identified weaknesses were the lack in organisational structure and hierarchy resulting in poor communication between departments, poor management of financial resources between departments causing some departments to benefit from the training opportunities more than others, and extreme lack in human resources resulting in heavy workloads.

The opportunities identified by the largest number of participants was the independence of the authority from the MOH, which gives the NHRA absolute power in providing advanced regulatory practices without interference of external interests. The NHRA's ability to expand and improve their regulatory services through knowledge transfer and sharing of best practices from the GCC Central Drug Registration meetings and collaborations with other international agencies was seen as a further important opportunity.

The threats mostly identified were the growing trade of counterfeit HMs worldwide, and the absence of a pharmacovigilance system in the NHRA to monitor adverse drug reactions. Some participants also described the threat of importation from countries with weak HMs regulations, and consumers obtaining unsafe HMs through the internet, where products are neither inspected nor assessed locally.

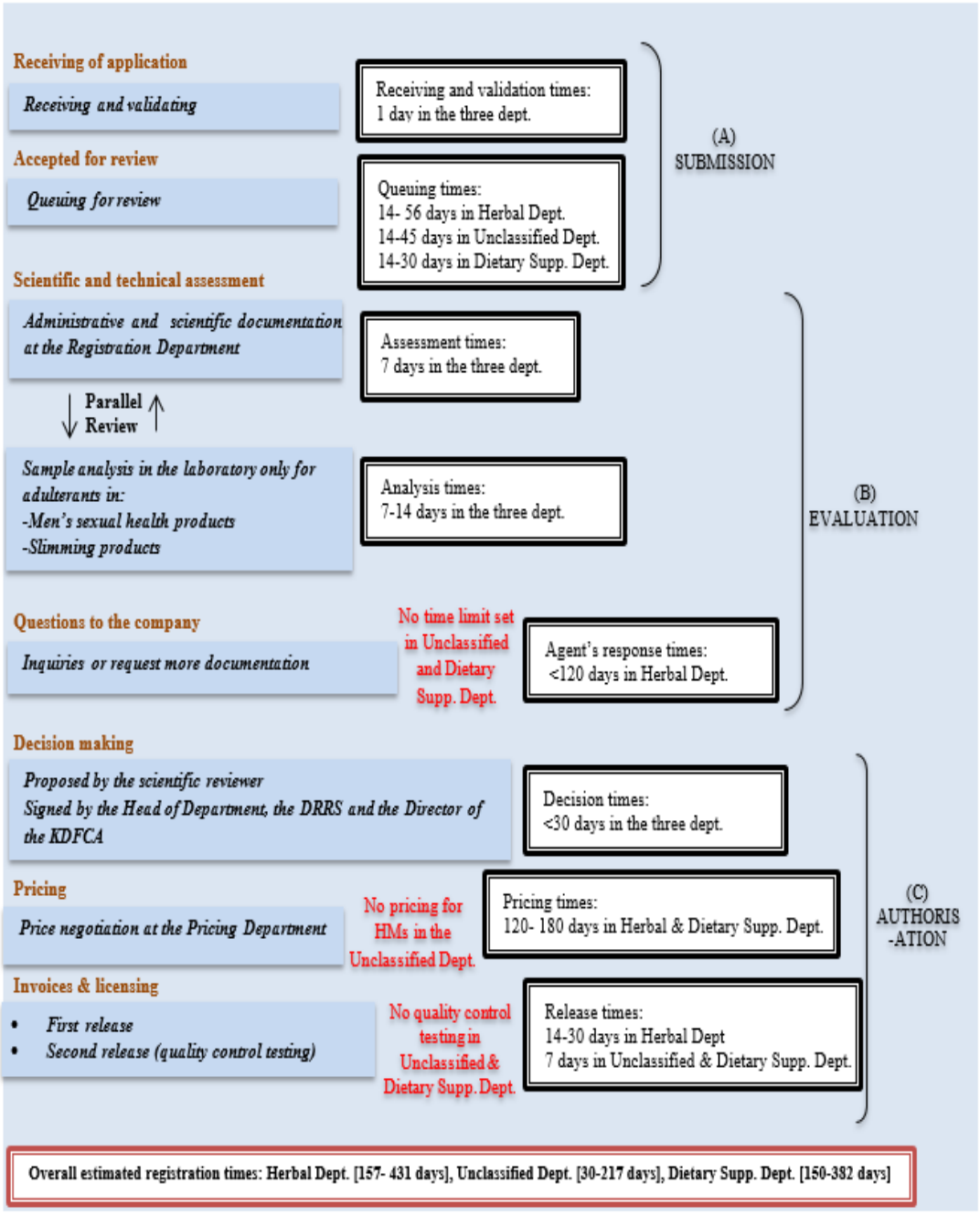
6.3.2 Case 2

6.3.2.1 The registration process of HMs in the Kuwaiti DRA

Following the detailed analysis of policy development, content and implementation in Bahrain, informed recommendation for an improved HM regulatory system. These recommendations were taken to Kuwait, case 2, where views on these recommendation were sought and the authority's readiness for change was also explored. Before this, participants were asked to describe the current system of HM regulation/ registration, and observations revealed that under the current system in the KDFCA, HMs can be allocated and reviewed in three departments; Herbal Department, Dietary Supplement Department and Unclassified Department (**Figure 6.4**). To facilitate effective comparison between the HM regulatory review in the three departments, the processes were divided into three phases, namely, A) submission, B) evaluation and C) authorisation. Overall, analysis showed that the regulatory process for HMs in the Herbal Department was more rigorous and therefore took longer than in either the Dietary Supplement or Unclassified Departments.

Unlike products at the Herbal and Dietary Supplement Departments that must undergo specific pricing procedure by the KDFCA, products registered at the Unclassified Department do not get priced by the KDFCA, but are priced according to the company's desires. For a full description of the regulatory process including similarities and differences in the HM process in the three departments, see Additional file 6.7.

Figure 6.4 Process map of HMs with estimated times in milestones, extracted from fieldnotes recorded during observation at the Herbal Department, Unclassified Department and Dietary Supplement Department in the Kuwaiti drug regulatory authority



DRRS Drug Registration and Release Superintendent, *KDFCA* Kuwait Drug and Food Control and Administration

6.3.2.2 Perceptions on the current system in the absence of a classification

All interviewees expressed concerns over the absence of a clear definition and classification procedure for HMs (**Table 6.3**). Many participants described that there was confusion on how to carry out the regulatory process despite the existence of the Ministerial Decrees, and that clear and decisive regulations were required so that incorrect and inconsistent decisions could be avoided. Moreover, many participants described their difficulties in deciding where to register products which included herbal and other ingredients such as vitamins and minerals. They explained that they did not have sufficient information to guide them nor were they able to use the regulations to *"back them up"* when agents and pharmaceutical companies argued to register products in certain departments.

Table 6.3 Perceived issues resulting from the absence of a clear definition and classification for HMs, with participants' quotes extracted from transcripts of interviews with officials at the Kuwaiti drug regulatory authority

Identified issues	Participants' quotes
Confusion on how to carry out the regulatory process	*"We are not sure that some products should be classified in the unclassified unit. So you see here there is a confusion. Reviewers are confused to where best classify the product because there is no clear guideline to follow. Sometime I am lost" (KI13)*
Difficulties in deciding where to register products that include a mixture of herbs and other ingredients	*"We receive products that contain many herbs and many vitamins, it is hard to make a conclusion whether this product is a herbal product or a vitamin product. What is happening that we are puzzled. How should we classify herbal products with vitamins? According to what? Is it according to the number of herbs? What if we receive a product that has a number of herbs are equal to the number of vitamins? And what about the pure herbs? "(K12)*
Participants feel that agents have more power	*"…the sad thing that the power of agents and companies exceeds our power. We are the supervisory authority, we should have the power" (KI17)*
Restrictions as a result of the term herbal medicine	*"The terms are restricting us. We do not have something called herbal supplement. When the agent hears the name medicine, they are frightened because this means stricter registration process so they go to the unclassified unit to register this herbal supplement" (KI22)*
Inappropriate pricing system	*"I do not get the concept of regulators in not forcing all products to be priced. From their point of view, they claim that dietary supplements are not a mandate; you do not take it to increase your life expectancy or to treat or cure a disease you have… people are taking them as a luxury. But if this is the case, then why do you price products in the herbal department? Not all of them are medicinal and not all of them have a medicinal use. My opinion everything must be priced" (KI16)*
The lenient regulatory process in the Unclassified Department	*"As a Herbal Department, we should have all herbal products that have purely herbal active ingredients registered here. The unclassified unit is here to provide a gap for agents instead of waiting a long time for their products to be registered at the herbal unit…" (KI10)*
Inconsistency and duplication in registration of many HMs with the same active ingredients and characteristics	*"What happens now is that the agent submits the product to the Unclassified Department while the product must be registered in the Food Department. And you find another agent, submits this exact active ingredient of a product in the food supplement and they both get registered but in different departments. But tell me, which one is the right department? How could we know for sure if we do not have clear regulation or information indicating what circumstances makes an herbal product a herbal medicine, food supplement or dietary supplement or even a vitamin" (KI16)*

HMs Herbal medicines

Moreover, other participants explained that due to the lack of clarity on what constituted a HM lead agents to register products according to their registration status in the country of origin. Because of lenient regulatory process in the Unclassified and Dietary Supplement Departments, where many HMs are marketed without testing, many participants considered the scientific analysis of products prior to market release as the most important requirement in order to maintain product quality and safety. In fact, many participants stated that all products should be classified and that the Unclassified Department should be removed. Some participants were against the MOH not pricing products in the Unclassified Department, as this meant that prices of unclassified products were very high, which they considered to be *"unjustifiable"* and that is *"not fair"* to consumers and patients.

A further problem that was identified by many participants was that different HMs with the same active ingredients and characteristics can be registered in more than one department, causing inconsistency and duplication in product registration. This led companies to complain about unfair and uncompetitive disadvantage.

6.3.2.3 Perceptions on implementing proposed recommendations

Having discussed views regarding the absence of a clear definition and classification for HMs, participants were asked about their opinions on implementing the proposed policy recommendations for HM definition and classification (Appendix 6.2), which had been given to them prior to the interview. These proposed recommendations aimed to promote harmonisation of HMs regulations, and were based on the findings from the five-country comparison [151] and the Bahraini case study 1. The recommendations consisted of 1) adopting a universal harmonised definition of what constitute a HM for the purpose of registration and specifying a directive that state that all herbal preparations matching the proposed definition must be assessed under one department, the Herbal Department, 2) under the Herbal Department, HMs should be registered under one of the two registration pathways a) Traditional Herbal Registration (THR) (simplified pathway) and b) Herbal Medicine Registration (HMR) (standard pathway), and 3) the decision for classifying a HM under either pathways depend on the ability to prove the product's efficacy (i.e. in THR 'plausible efficacy' due to established history of traditional use is sufficient to assure efficacy, whereas, HMR requires full registration similar to a conventional medicine registration requiring a marketing authorisation and proven clinical efficacy).

Overall, there was real enthusiasm about introducing a HM classification policy by almost all interviewed participants and they described it as an *"urgent need"*. Some of the expressions were:

> *"This is an excellent idea. This will solve many problems. You are not proposing that these products are registered straight away, this only means that following the guideline we classify the products in the right department" (KI16) "We need it [classification policy]. I totally agree" (KI15) "…from the beginning of the registration, it is much, much better that a product be classified" (KI20)*

However one participant believed that a classification policy was not needed in Kuwait, due to restrictions this would impose. This participant felt that reviewers were experienced enough to make the right decision, and that Kuwait, as an importing country, should be align with the product status in the country of origin. The remaining participants described the benefits (**Table 6.4**) as saving time for both reviewers and agents by allocating the HM to the right department at the start, consistency in the HM registration process, increasing reviewer's confidence in making decisions and improving consumer's safety by assuring that all HMs are assessed correctly before marketing.

Table 6.4 Perceived benefits for implementing the proposed recommendations of a HM definition and classification, with participants' quotes extracted from transcripts of interviews with officials at the Kuwaiti drug regulatory authority

Benefits	Participants' quotes
Saving time for both reviewers and agents	*"…it will help and solve a lot of problems, and will assure us and the agents, that the product is registered under the correct registration department with the correct requirements from the beginning of registration,* and *products will not be transferred from one department to another in order to make a decision." (KI12)*
Consistency and clearness in the HM registration process	*"I think this [classification policy] will make things easier and clearer. Today, to be honest, there is confusion and disorder in classifying products. Look, to be honest, during one year, many products were transferred, and most of them because of the complaints of big companies against their competitors. And if it wasn't them, nothing will be changed. So this [classification policy] will change many things and will put things into order" (KI10)*
Increasing reviewer's confidence in making decisions	*"I noticed something else that agents, once you tell them that this is a policy or this is a guideline… well, this is out of my hands, they actually adhere with you. But if there is no policy or no guideline, even if you told them many times, well, this shouldn't be registered here, they won't listen to you because there is no proper guideline they have to follow" (KI14)*
Improving consumer's safety	*"Our requirements for herbals [in the Herbal Department] are excellent very strong requirements, almost similar to the pharmaceutical registration requirements so if all HMs are registered here this will make sure that side effects are less to appear and this will increase the safety of consumers" (KI11)*

HMs herbal medicines

Contextual factors of the readiness for implementing the proposed recommendations

Participants were asked to provide their views on the five contextual factors informed by TORC that would affect the authority's readiness to implement the proposed recommendations; a) policies and procedures, b) past experience, c) organisational resources, d) organisational culture and e) organisational structure. For identified sub factors and participants' quotes, see Table 6.1 in Additional file 6.8.

Policies and procedures

Many reviewers stated that the authority's management lacked motivation to introduce new policies, because employees are promoted as a result of the number of years they have worked for the authority rather than the quality of their work and ideas they proposed. Some interviewed reviewers suggested that incentives may be helpful, and that management may benefit from the inclusion of different, younger people who may be more motivated to introduce new ideas that suit the new era. Indeed new staff had recently been recruited for management positions, and interviewees were optimistic that the system would improve as a result of this.

Views between interviewed reviewers and management differed regarding the level of their involvement with each other when developing policies. Most reviewers considered their involvement in policy development as important. Yet reviewers feel that their views were not encouraged by management who did not value their specialised opinions. Management, however confirmed that they would include whoever was necessary in the policy development process.

Decision-makers were also asked to share their views regarding the process of approving a HM classification policy. They viewed updating the current Ministerial Decree as the best approach; they also agreed that the power to impose penalties would give the authority the power over agencies and companies who were non- compliant. Many participants agreed that parliament should consider separating the KDFCA from the MOH to become a fully independent authority and give the KDFCA the autonomy to improve and implement regulations without the need for the lengthy process approval.

Past experience

Participants were asked about issues that, based on their past experience, would need to be considered before policy implementation. Most participants emphasised the authority looking into the different regulations in different countries and prepare a policy that was compatible with international regulations. Other participants added that the authority must consider the exporting countries' classifications. Many participants also stated that it would be essential to have continuous discussions and regular meetings with the employees who would be implementing the policy to discuss any issues they encountered. Participants also stressed the importance of regularly reviewing the policy according to international policies to ensure it remained up-to-date.

All participants recognised that the introduction of the classification would result in agents disagreeing with the decisions made, which they would try to change. Participants therefore suggested an implementation period for agents to get used to the requirements. Some participants also recommended that there should be a formal right to appeal on decisions made, as this would give agents a level of advocacy. Publication of the policy on the authority's official website was seen as further increasing both transparency and compliance.

Organisational resources

Once the HM classification was in place, many products previously registered under the Unclassified or the Dietary Supplement Departments would need to be re-classified. Therefore, many participants considered it to be essential to increase the number of reviewers, particularly as the authority already faced significant staff shortages. Other participants stated that it would be vital to also have herbal specialists who understand the science behind herbals and are able to solve confusion which may occur.

All participants noted that reviewers would require training, including on international guidelines and regulations in HMs from other countries. All participants recognised that the implementation would require financial resources to ensure enough staff, training courses and technical methods. Some participants did not consider this a strain, because the MOH held a significant amount of financial resources.

Organisational culture

All participants described what is known as mediation or favouritism; giving preferential treatment to one person at the expense of another, are cultural norms which also impact regulatory decision- making. Many participants recognised that in order to overcome these cultural challenges, it would be important to appoint people with high integrity and honesty. Other participants suggested that one way of dealing with the risk of mediation and favouritism was to appoint more than one reviewer to decide on the classification of a HM.

Moreover, many participants described that the current system whereby agents simply turning up without appointments was not conducive to an independent and organised workflow. Having to respond to agents at any time caused reviewers stress and meant there were no clear boundaries between agents and reviewers. They recommended that there should be a separate office or reception that welcomes agents, deals with their requests, and organises appointments for receiving files.

Organisational structure

Some participants thought that the implementation would require organisational restructure, others did not. Those who advocated a new structure suggested that it would be essential to introduce the policy with a separate classification department that is only responsible for classifying products.

6.4 Discussion

This study used Anderson's conceptual model for policymaking [15] to analyse the Pharmaceutical Product Classification (PPC) policy in Bahrain, including the system's strengths and weaknesses, which informed recommendations of a suitable HM classification procedure for Kuwait. These recommendations were then used to explore Kuwait's readiness towards implementing. Each of Anderson's steps applied a policy model to guide study design and frame analysis, which delivered a valuable and novel procedure for analysis and interpretation.

Case 1 provided insights in the policymaking process of the PPC policy in the Bahraini DRA and showed that contextual factors were important catalysts to setting the NHRA's agenda in improving their policies, particularly the separation of the authority from the MOH and a desire to establish an internationally recognised robust

system. The importance of the involvement of international experts in the policy process was also revealed, which played a major role in agenda setting and adoption of a policy which outlines criteria for classification decisions and solve HMs registration issues. In combination with a five country comparison [3], the findings from case 1 informed recommendations for a suitable definition and classification procedure for Kuwait which is similar to the European Directive on Traditional Herbal Medicinal Products and the Bahraini PPC policy [3]. Specifically, the recommendations were to adopt a harmonised definition of what constituted HMs, and to introduce a Traditional Herbal Registration, to ensure that the efficacy of traditional herbal medicinal products is considered plausible without the need for conducting extensive clinical studies. These recommendations were used in case 2 to investigate the Kuwaiti authority's readiness for implementation, which revealed positive responses and high motivation from officials.

Both the logic and research evidence in policy implementation and readiness for change have concluded that there is a high chance of implementation success if the members' willingness to adapt to the change is high [32, 47]. However, other features also have a great influence on the success or failure of policy implementation [18, 19, 48, 49]. Using perspectives in literature and insights into the two investigated cases, five common features were identified which the Kuwaiti DRA must consider. These features are: management support and leadership, employees' involvement in the policymaking process, organisation cultural context, implementation planning and allocation of resources, and the organisation's autonomy.

Leadership in management is important in providing commitment, motivation and direction to employees [50, 51]. From case 1, the Bahraini DRA had leading management figures who engaged with reviewers and motivated them throughout the policy change process. In case 2 however, reviewers raised a lack in communication and appreciation of management, which ought to change in Kuwaiti DRA management, so that leadership can inspire employees and engage them in the change initiatives.

Involving employees in the policymaking process aligns with Hajar and Weagenaar, who note that policymaking has to become more interpretive (less top down), involving people's stories, views and beliefs [52]. In case 1, the Bahraini DRA involved all reviewers in the development of the policymaking processes, making it easier for reviewers to understand and implement the policy in practice. In case 2,

reviewers explained that they currently have limited opportunity to interact with management, but interviews with management indicated that they would involve relevant reviewers in the development of the policy.

Pharmaceutical industry gain significant profits following successful registration and pricing of their products, and their interests have been perceived to influence the policy implementation significantly [39]. In case 2, resistance of agents and pharmaceutical companies to changes and the impact of cultural and traditional ways of working was affecting some important regulatory decisions in the Kuwaiti DRA. In case 1 however, Bahrain DRA's decisions were based on a clear system and transparent regulatory procedure with the final decisions performed collectively through a committee which made it difficult for agents and pharmaceutical companies to modify or influence regulatory decisions. These features could be adopted by the Kuwaiti DRA to prevent the possibilities of conflicts of interest and/or the culture of favouritism and corruption entering the system. Moreover, to increase compliance, similarly to the Bahraini DRA, the Kuwaiti DRA should consider binding the guideline to a decree, so that employees and agents are legally obligated to comply with the content of the guideline.

Before any attempt for implementation is made, it is important that resources for potential and projected implementation needs are identified and anticipated [32]. In Case 1, policy reflected the "quick-fix" mentality of policy-makers [53] which meant setting an implementation plan was neglected. This resulted in implementation challenges, such as lack of expertise in HMs, lack of regular training, and workload due to limitation in staff. Case 2 indicated that there was potential for similar challenges upon implementation which would need to be considered. Identifying appropriate monitoring and evaluation measures for implementation including allocation of evaluation responsibilities and monitoring resources, also need to be addressed in the planning phase [54]. In case 1, although the Bahraini DRA conducted evaluation of the PPC policy by calculating the number of successful products applications prior and following implementation of the policy, the evaluation did not specify the number of successful classifications for HMs alone, but included all product types without specifying the number of each type. Other critical evaluation aspects that the Bahraini and the Kuwaiti DRAs should consider include obtaining reviewers' and local agents' feedback (e.g. through questionnaires, complaints, meetings or workshops), and undertaking inspections to monitor classification

consistency, accuracy and compliance through observing reviewers' performance and tracking of applications [55].

Case 2 exemplified that one of the main deficiencies in policies is because the Kuwaiti DRA is structurally, administratively and financially under the autonomy of the MOH, slowing down policy development and implementation. However, Kuwait's regulatory authority works independently from all the other divisions and departments within the MOH, which leads to it important role not being sufficiently recognised by the government. This makes it very difficult for the regulators to persuade the MOH to improve and approve the policies within the Kuwaiti DRA [56]. In case 1, the separation of medicines regulation from the MOH provided the Bahraini DRA the autonomy to produce regulations and approve them without the interference and the lengthy process of approving them through the MOH. It is therefore recommended that the Kuwaiti government considers separating the Kuwaiti DRA from the MOH to become a fully independent authority.

This study has several strengths. In both cases, the investigation of the regulatory processes triangulated the findings from three different sources, namely documents, direct observations and in-depth interviews to provide an accurate picture of the regulatory processes and staff experiences in each regulatory authority. Moreover, there was a high participation rate, with all key officials involved in the HM registration process in both authorities participating.

The study has a number of limitations. First, in case 1 recall bias could be an issue, as participants had to retrospectively reflect on the policymaking and implementation process of the PPC. However, recall bias was counteracted by validating findings by document review. Second, in both cases it was not feasible to observe individual products, and in both cases, timelines were estimated but not validated. Finally, as both cases only targeted participants who work directly with HMs, the views of other stakeholders such as agents and consumers were not explored.

6.5 Conclusions

Increasing consumer demand for HMs, and possible undesirable effects resulting from the consumption of HMs, necessitated that national DRAs sensibly update their HM policies to safeguard the public. This study makes a unique and novel contribution to the HM policymaking literature by generating insights from one of the DRAs (case 1:

Bahrain) which had recently updated their HM registration system. Using Anderson's policymaking steps, a detailed analysis of policy development, content and implementation in the Bahraini DRA (case1), together with a previous document analysis that investigated HMs laws in advanced systems, provided evidence-based lessons for effective HMs regulation. The recommendations included a clear definition of what constitute HMs, and an introduction of a Traditional Herbal Registration based on this definition and the product's characteristics. Subsequently, these recommendations were examined for implementation readiness in an unsophisticated HM system in Kuwait (case 2), concluding that the potential implementers' readiness for implementation was high.

It is anticipated that lessons from both case studies can help guide other countries with improving their HMs policies. Study methodology can be adopted in future policy case studies including comparative case studies. Future research could incorporate the views and perceptions of other stakeholders such as HMs users, agents who register HMs and manufacturers/ industry.

Ethics approval and consent to participate The study was approved by the University of Manchester Research Ethics Committee (UREC)–Project Number: 2017-1086-3939, and permissions to conduct research at the Bahraini and Kuwaiti DRAs was obtained from each authority. All participants gave informed consent, each participant was assigned a unique code, and anonymity was maintained at all times during the research process.

Consent for publication Not applicable.

Availability of data and materials
The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests This is an independent research undertaken as part of a PhD, and the authors were not asked nor commissioned to inform a herbal medicine registration system for the Kuwaiti drug regulatory authority (DRA). However, it is projected that the recommendations generated from this research will be proposed to the Kuwaiti DRA for consideration.

Authors' contributions AA, DS, ES: study concept and design. AA: data extraction, analysis and writing of manuscript. DS, ES: revision of manuscript and ES providing significant input. All authors: reviewed the manuscript and agreed with the decision to submit for publication.

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Additional file 6.1: Description of data sources used in the illustration of findings in case 1 and case 2

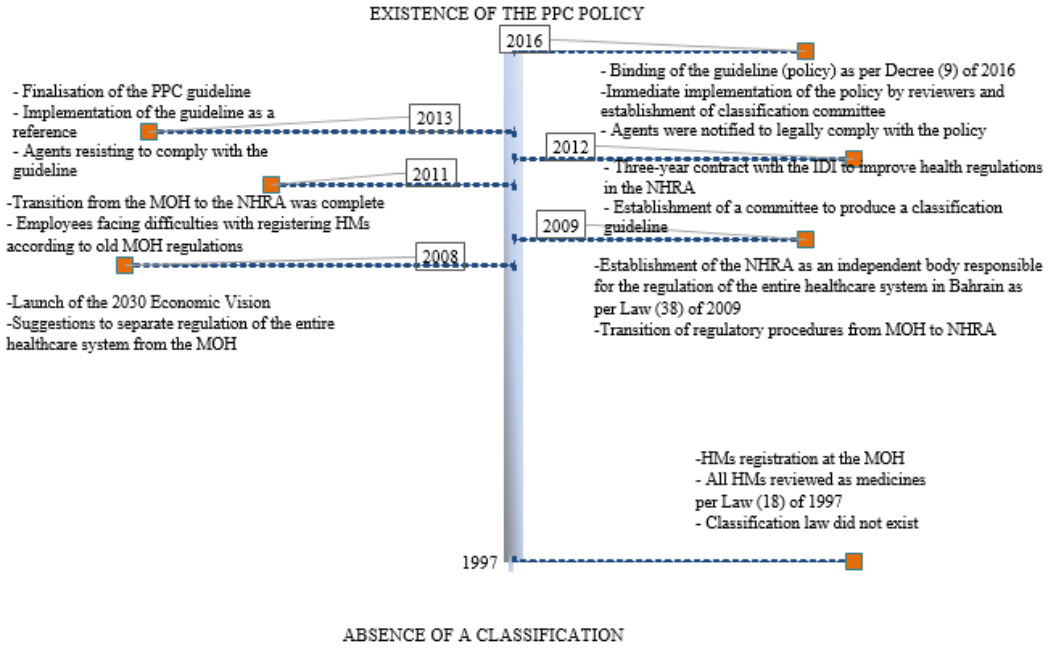
Table 6.1 Description of sources of data used in each case

Cases themes		**Sources of data used**
Case 1	Context, Actors, Content and Process in the development and implementation of the PPC policy in the NHRA	Data from interviews with 5 reviewers (KI1, KI2, KI3, KI4, KI5) and 3 managers (KI6, KI7, KI8) Document review of the Economic Vision 2030, Law (18) of 1997 With Respect the Practice of Pharmacists and Pharmaceutical Centres, IDI Technical Support Services for the Development, Operations and Management of the NHRA, Decree (9) in relation to Classifying Pharmaceutical Products and Health Products, Health Products Checklist, Medicines Checklist, Strategic Plan (2016 2020) and NHRA annual report 2016, Pricing Guideline
	The registration process of HMs in the NHRA	Field notes from10 observations of 5 reviewers (KI1, KI2, KI3, KI4, KI5) Document review of PPC guideline (2013), health products registration requirements, medicines registration requirements and Pricing Guideline
	SWOT analysis for the HM registration system in the NHRA	Data from interviews with 5 reviewers (KI1, KI2, KI3, KI4, KI5) and 3 managers (KI6, KI7, KI8)
Case 2	The registration process of HMs in the KDFCA	Field notes from 19 observations of 9 reviewers (K19, KI10, KI11, KI12, KI13,KI14, KI15, KI16, KI17) Document review of Herbal Department Ministerial Decree (201/97), Dietary Supplement Department Ministerial Decree (532/2002), Unclassified Department Ministerial Decree (201/99)
	Perceptions on the current KDFCA's HMs registration system and readiness towards implementation	Data from interviews with 9 reviewers (K19, KI10, KI11, KI12, KI13, KI14, KI15, KI16, KI17) and 6 Managers (K118, K119, K120, K121, K122, K123)

HM herbal medicine, *IDI* International Development Ireland, *KDFCA* Kuwait Drug and Food Control and Administration, *NHRA* National Health Regulatory Authority, *PPC* Pharmaceutical Product Classification, *SWOT* Strengths, Weaknesses Opportunities and Threats

Additional file 6.2: An analysis of the Context, Actors, Content and Process in the development and implementation of the Pharmaceutical Product Classification policy in the Bahraini drug regulatory authority

Figure 6.1 Chronological progress of the Pharmaceutical Product Classification policy at the Bahraini drug regulatory authority

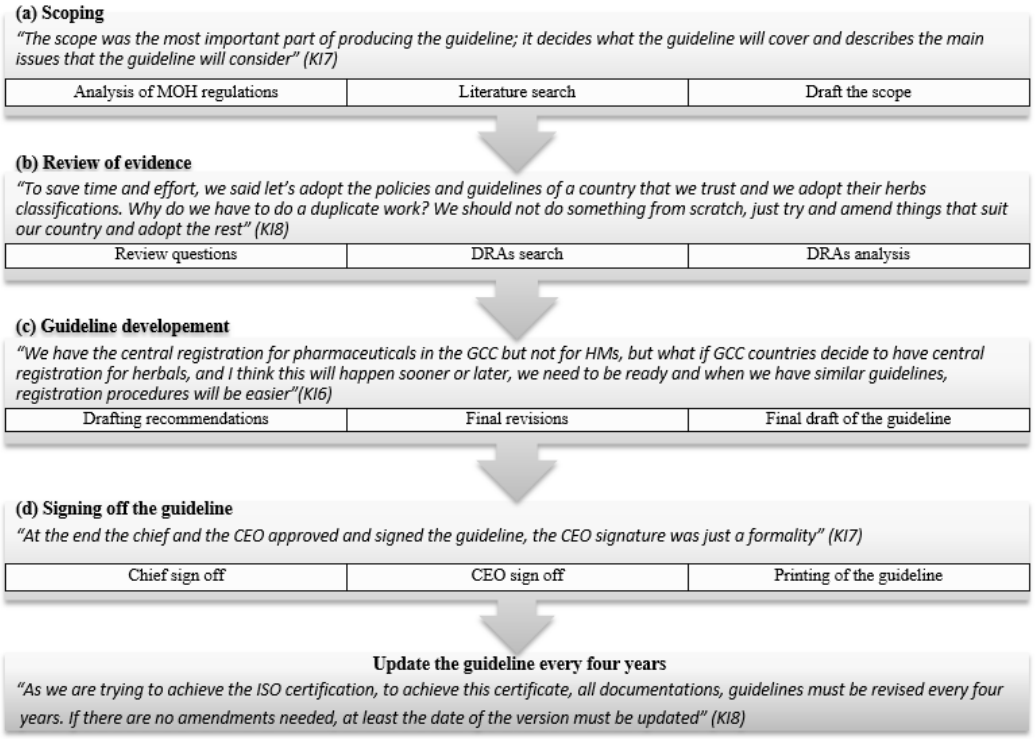


HMs herbal medicines, *IDI* International Development Ireland, *MOH* Ministry of Health, *NHRA* National Health Regulatory Authority

Additional file 6.2: Data from the analysis of collected documents and interview transcripts on the chronological progress of the Pharmaceutical Product Classification policy in the Bahraini drug regulatory authority

Additional file 6.3: An analysis of the production stages of the Pharmaceutical Product Classification guideline at the Bahraini drug regulatory authority

Figure 6.1 Production stages of the Pharmaceutical Product Classification guideline at the Bahraini drug regulatory authority, with participants' quotes



CEO Chief Executive Officer, *DRAs* drug regulatory authorities, *GCC* Gulf Cooperation Council, *HMs* herbal medicines, *ISO* International Organisation for Standardisation, *MOH* Ministry of Health

Additional file 6.3: Data from the analysis of interview transcripts on the production stages of the Pharmaceutical Product Classification guideline at the Bahraini drug regulatory authority

Additional file 6.4: An analysis of facilitators and barriers in the development and implementation stages of the Pharmaceutical Product Classification policy in the Bahraini drug regulatory authority

Table 6.1 Perceived facilitators in the development stage of the Pharmaceutical Product Classification policy at the Bahraini drug regulatory authority, with participants' quotes

Themes	Facilitators	Participants quotes
Management and collaboration	NHRA seeking to build good reputation as a newly established entity Coordination with external organisations Teamwork among NHRA officials and external experts	*"We learned from them [external experts] so much. They were very open in sharing their knowledge and the communication with them was easy. You know we had the chance to benefit from great minds so we tried to benefit from this as much as we can" (KI7)*
Leadership	Key figures planning and guiding the development process and providing officials with support and encouragement	*"We had continuous support from the CEO she understands us and she supported us" (KI5)*
Resources	Availability of funding Availability of skilled external experts Availability of data and informative DRAs websites	*"To be realistic, financial support it was the most important part, because there would be no contract with the Irish group without money, and without the experts it would be difficult to make the guideline" (KI1)*
Nature and content of the policy	Not mentioned	
Political and social influences	Incoherent existing policy causing controversy and existing of international classification policies in other countries providing justification for the decision to issue a classification Bahrain being a member of the GCC facilitating communications and inquiries with other members	*"Being part of the GCC and during our communications with the GCC countries for central registration, we learned that certain guidelines must exist which will make our life easier, and availability of a classification system in Saudi Arabia helped a lot "(KI8)*
	NHRA independence and freedom from the political and commercial influence of the MOH	*"We are independent from the MOH, so the production of new policies and guidelines doesn't require the MOH approval and the long process of approving polices. Internally at least we can produce our own policies and guidelines and the MOH can't interfere with this" (KI4)*
	SCH support in approving the policy efficiently	*"We are not alone, we have the support of the Supreme Council, and they strengthened our role as an independent organisation and they enabled all our regulations to come into action very quickly. We felt that they had our back" (KI7)*
Staff morals and performance	Commitment of committee members in finalising the production of the guideline on time	"*To be honest, we were efficient; we worked very hard to accomplish the guideline. We had consistent meetings, sessions after sessions, with dedication and team-work effort it was possible to deliver the guideline on the right time" (KI7)*

DRAs drug regulatory authorities, CEO Chief Executive Officer, GCC Gulf Cooperation Council, MOH Ministry of Health, NHRA National Health Regulatory Authority, SCH Supreme Council of Health

Table 6.2 Perceived barriers in the development stage of the Pharmaceutical Product Classification policy at the Bahraini drug regulatory authority, with participants' quotes

Themes	Barriers	Participants quotes
Management and collaboration	Not mentioned	
Leadership	Not mentioned	
Resources	Lack of sufficiently trained and experienced NHRA staff	*"Our experience in Chemistry and conventional medicines is more than herbals. Establishing classification or even policies to regulate herbs is extremely difficult; the topic is not just black and white, it is a complicated subject and we don't have the expertise. Unfortunately, we didn't receive training on decision-making techniques. It all depended on our personal effort and reading and asking other experts" (KI3)*
Nature and content of the policy	Diversity of worldwide herbal regulat lack of a universal classification for HM	*"The problem with herbs that, for example USA licenses it as food supplement, UK however classify it differently, we import our product from both countries, how could we adopt a reasonable classification?" (KI1)*
Political and social influences	Not mentioned	
Staff morals and performance	Not mentioned	

HMs herbal medicines, *NHRA* National Health Regulatory Authority, *UK* United Kingdom, *USA* United States of America

Table 6.3 Perceived facilitators in the implementation stage of the Pharmaceutical Product Classification policy at the Bahraini drug regulatory authority, with participants' quotes

Themes	Facilitators	Participants quotes
Management and collaboration	Teamwork and cooperation between officials	*"We see each other more than we see our family; we spend more hours during the day with each other than our families, so we respect each other very much this is important we also helped each other, if I was sick, my colleague would cover my duties until I come back. I did the same. When you work in a workplace like this, it makes it easier to implement procedures effectively" (KI2)* *"We as a team used to meet once every two weeks to see how the implementation is going and whether any difficulties has occurred while implementing it through receiving the files and classifying the product… We keep records of cases we can't classify with the guideline so we don't forget when we update the guideline" (KI4)*
	Setting an adaptation period for pharmaceutical companies to comply with the new system	*"We gave them [agents] some time to provide us with the requirements for their registered products according to the new guideline. We understood it is new for them, we gave them some time to understand and cope" (KI3)*
Leadership	Effective internal leadership and support from key figures	*"The role of the CEO normally is to stand at the top of the pyramid and the rest takes order, our CEO is different, she helped us with difficult registration issues, even with the guideline sometimes we had to make different decisions"(KI2)*

Resources	Availability of international references and availability of informative international DRAs' websites No training was required on how to implement the policy	*"I was searching a lot online because when you search you find everything you need. Overall if we don't have a reference for some product or information is not in the guideline, or we are unsure, we always check our referenced trusted authorities' websites" (KI1)* *"Already the reviewers that needs to implement the guideline in practice were involved in the production process, so they are aware of the guideline and understands how to implement it effectively. They [old reviewers] taught the new reviewers everything, how to use the guideline and why it is important that they use it" (KI7)*
Nature and content of the policy	Availability of a clear guideline The guideline being based on classifications of countries that Bahrain imports from	*"It is really great to have a guideline it makes my life easier. You can't always depend on other countries' websites, sometimes you need your own guideline. A lot of information inside the guideline is from countries we import from, so it is easier when we request for documents. The guideline is here to help us as regulators and help the agents as well. For agents, you can't just submit something and just wait it might be accepted or rejected, there are specifications, knowing where the product can be classified from the beginning saves a lot of time and effort" (KI1)*
Political and social influences	Inability of the MOH to influence decisions made by the NHRA Binding the guideline and forcing sanctions on violators	*"The separation from the MOH increases the integrity of the drug regulatory and gives protection from interference of special interests… We also enforced penalties on anyone who try to break up this regulation or other regulations as well, so people are really careful to comply" (KI8)*
Staff morals and performance	Staff motivation and devotion to effectively implement policies in order to protect the public	*"You need excellent reviewers, but you also need reviewers who are dedicated to make the implementation work" (KI8)*

CEO Chief Executive Officer, *MOH* Ministry of Health, *NHRA* National Health Regulatory Authority

Table 6.4 Perceived barriers in the implementation stage of the Pharmaceutical Product Classification policy at the Bahraini drug regulatory authority, with participants' quotes

Themes	**Barriers**	**Participants quotes**
Management and collaboration	lack in providing a clear plan for policy implementation and allocation of resources	*"We barely had the time to finalise the guideline, we needed it urgently, we thought that as soon as we have it we will use it and it will solve many problems, and it did solve many problems, but yes we should've had a better plan to make the implementation work even better"(KI6)*
Leadership	Not mentioned	
Resources	Lack of expertise in HMs	*"Herbs are the most difficult products that we have. We need expertise, which we do lack right now. That's why we depend on external regulations" (KI8)*
Nature and content of the policy	Diversity in HMs classifications worldwide and the continuous change in HMs regulations	*"HMs regulations keep changing. Of course it needs improvements, but even with this second version guideline, I think that it still needs improvements. But I can't make any further improvements because the problem is that every country has its own method of assessment and their own classification system, with the same herb you find it banned in one country, but another country it is classified as health product, even the type of classification is different. For example*

	No use of scientific evidence in the development of the policy	*some country has what is called "traditional herbal medicine" other countries don't" (KI6)* *"The Irish reference states that a product cannot have more than five herbs in it. If it does then it will not get registered as HP, but as a medicine. We searched this information, we couldn't find that reference other than Saudi Arabia who had it as well, but based on what, this we couldn't know. So we are changing this rule now" (KI7)*
Political and social influences	Resistance from agents to comply with the new system	*"It is taking them [agents] a long time to adapt; we still face issues with agents not aware of the current regulations. But we are getting there, change needs time" (KI4)*
Staff morals and performance	Not mentioned	

HMs herbal medicines, *HP* health product

Additional file 6.4: Data from the analysis of interview transcripts on perceived facilitators of, and barriers to the development and implementation of the Pharmaceutical Product Classification policy in the Bahraini drug regulatory authority

Additional file 6.5: An analysis of the classification and registration process of herbal products and herbal medicines at the Bahraini drug regulatory authority, including similarities and differences between the two pathways

(A) Classification

The agent can request for a classification appointment using the online Pharmaceutical Product Classification (PPC) application at the National Health Regulatory Authority's (NHRA) website. The agent is given an exact time and date to submit materials consisting of signed and stamped cover letter and application form, artwork of the product's outer-packaging and inner label, copy of the composition certificate issued from the manufacturing company, one product sample and a payment of 50 USD. On the day of the appointment, the reviewer validates submitted materials and prepares a report stating an initial classification decision whether the product should be classified as a herbal medicine or a herbal product upon interpreting the totality of four factors based on the PPC policy.

1) If the product explicitly claims to treat or prevent a disease, it will be considered as a herbal medicine and any claims made for herbal products should be consistent with available evidence regarding the safety and traditional use of those products e.g. published peer-reviewed scientific literature. 2) Herbal products cannot be sterile, and/or administered by injection and products with these characteristics will be considered as herbal medicines. 3) If the product is subject to a medical prescription or/and requires the intervention of a healthcare practitioner, the product will be considered as a herbal medicine. 4) The classification guideline contains a list of herbal substances, which are considered not suitable as herbal products but may be considered as herbal medicines.

The classification committee consisting of the reviewer responsible for the product's classification, an external specialist (depending on the nature of the product) and a senior pharmacist makes the final classification decision. The decision is made upon reviewing the reviewer's report ensuring that the product is classified according to the most suitable classification based on the four classification factors. Overall, it takes approximately one month for the product to be classified in the NHRA. Once the product is classified, it must be submitted for registration in the related department.

(B) Submission

Similar to classification, for herbal medicine or herbal product registration, the agent must request an appointment through the NHRA official website to submit administrative, quality, safety and efficacy requirements documents to the relevant department.

Table 6.1 Similarities and differences in the registration requirements of herbal products and herbal medicines extracted from Law (18) of 1997 With Respect the Practice of Pharmacists and Pharmaceutical Centres

Regulatory requirements	Herbal product	Herbal medicine
Administrative		
Legalised Good Manufacturing Practice Certificate	✓	✓
Finished product sample and leaflet	✓	✓
Original Legalised Free-Sale Certificate or Certificate of Pharmaceutical Product	✓	✓
Original legalised Price Certificate	**X**	✓
Quality		
Certificate issued by the company stating that the product does not contain or contains the allowed percentage of heavy metals	✓	✓
Certificate of Suitability for the active substance	**X**	✓
Raw materials specifications	**X**	✓
Finished product specifications	✓	✓
Composition of the product	✓	✓
Certificate of Analysis	**X**	✓
Stability study	**X**	✓
Declaration of alcohol and deceleration of pork free content	✓	✓
Safety and efficacy		
Clinical studies/ scientific references	✓ (scientific references)	✓ (clinical studies)

Requirements for herbal products are less demanding than of herbal medicines (**Table 6.1**). For example, unlike the herbal medicine, a herbal product does not require clinical studies to demonstrate its safety and efficacy, the submission of published scientific references stating the traditional use is sufficient.

On the appointment day, the reviewer validates the submitted documents and divides it into two sections, the safety and efficacy section which is queued for reviewing by the scientific reviewer and the quality section which is queued for assessing in the laboratory.

(C) Evaluation

Two evaluation routes for herbal medicines and herbal products registration exists in the NHRA; the verification and the abridged evaluation.

The Verification evaluation route is used to reduce duplication of effort by agreeing that Bahrain will allow herbal medicines and herbal products to be locally marketed once they have been authorised by two or more recognised competent regulatory authorities in countries such as Australia, Canada, United Kingdom, and some countries in Western Europe. In this route, the reviewer only 'verifies' that the product intended for registration has been duly registered as declared in the application and that the product characteristics (formulation composition) and the presenting information (use, dosage, precaution) for local marketing conforms to that agreed in the reference authorities.

The Abridged evaluation route applies to herbal medicines and herbal products that do not fall under the verification route. However, it conserves resources by not re-assessing all scientific supporting data that have been reviewed and accepted elsewhere, but includes an 'abridged' independent review of the product in terms of its use under local conditions, this might include review of the climatic conditions, benefit risk assessment in relation to use in local ethnic population, cultural/medical practice and patterns of disease and nutrition. It is a requirement that the product is registered for a minimum of twelve months in the country of origin and approval by a recognised regulatory authority elsewhere is pre- requisite before the local authorisation can be granted. In both routes, an assessment template is completed by the appointed reviewer.

In both pathways, products samples are sent to the laboratory for chemical and physical analysis as per their finished product's specifications. Most agents request that samples are analysed in a private laboratory (analysis takes fifteen days) which is accredited by the NHRA to avoid long waiting periods that might take up to three months in the governmental laboratory. No interaction is allowed between the agent and the laboratory and once results are completed and open for review, they are sent directly to the responsible reviewer.

Once the scientific and laboratory assessment of the product is complete, queries or concerns relevant to the product's quality, safety and efficacy are generated. The queries are sent to the agent by the reviewer electronically through completing an Information Request Form (IRF).

(D) Authorisation

Once herbal medicines have been assessed and tested, the product is transferred to the pricing department and a certain price within the required limits must be assigned according to the Pricing Guideline's formula; if the herbal medicine costs less than 50 USD, the profit margin is 35%, and if the medicine costs more than 50 USD, the profit margin is 20%. Herbal products are not priced, and the agent can freely price the product without any restrictions.

The final decision to approve a herbal medicine or a herbal product is carried out by the licensing committee, which consist of a senior pharmacist, the reviewer who reviewed the file, the Chief of the Pharmaceutical Product Regulation Department and an external reviewer. An assessment template completed by the appointed reviewer during the assessment stage is presented to the committee to provide a standardised content and format of the data and shows the reviewer's recommended decision. The committee evaluates the report and the final decision is made collectively. An approval certificate is then issued and signed by the Chief of the Pharmaceutical Product Regulation Department.

Upon approval of the committee, the agent can import the product's shipment from the country of origin. The NHRA follows the Invoice Clearance Procedure Guideline to release herbal products and herbal medicines into the market.

Additional file 6.5: Data from the analysis of fieldnotes and documents on the classification and registration process of herbal products and herbal medicines at the Bahraini drug regulatory authority

Additional file 6.6: An analysis of Strengths, Weaknesses, Opportunities and Threats of the current HMs registration system at the Bahraini drug regulatory authority

Table 6.1 Perceived Strengths, Weaknesses, Opportunities and Threats in the current HMs registration system at the Bahraini drug regulatory authority, with participants' quotes

Strengths (internal conditions)	**Participants quotes**
Motivation of the regulatory authority to improve making it a trustworthy authority	*"We are aiming to be number one regulatory authority in the Gulf, so we are always trying to improve our procedures, our system, going over old policies and advance them" (KI3)*
Transparency and honesty of the review procedure	*"We make sure that we are transparent as much as possible, this is very important to gain public trust" (KI8)*
Existence of committee for scientific assessment	*"The final decision for approving medicines are made by the scientific committee, this has the advantage of ensuring the availability of experienced staff and discuss issues that may not be tackled by only one reviewer" (KI1)*
Availability of guidelines and SOPs	*"We have guidelines, we follow our own SOPs, we have registration requirements that are clear, these helps a lot, they help us carryout the registration procedure consistently "(KI8)*
Availability of an electronic system	*"Having an electronic system to register and track applications, to record decisions of applications and you, this provide better handling for information and saves time" (KI6)*
Weaknesses (internal conditions)	**Participants quotes**
Lack in the organisational structure and hierarchy	*"I think that the organisational structure could be improved to give a higher authority to certain positions. For example, the structure needs to be more hierarchal, there is still some gaps in the structure of the different departments of the Pharmaceutical Product. I think it is better to have one manager for each department, like for HPs, medicines, renewals and so on, like this I think it is easier for reviewers to reach their managers instead of having one manager for all departments" (KI2)*
Lack of training in HMs regulations	*"We do have financial resources but it is very restricted and for all employees under all departments in the NHRA not specifically for Pharmaceutical Product department. And what happens is that the [names another department in the NHRA] takes the most of the training being a newly established department that needs improvements. How can I improve the authority without continuous training and continuous knowledge about what is happening in the regulatory aspects worldwide?" (KI3)*
Extreme lack of human resources	*"The extreme limitation in staff is becoming a serious problem, it's causing us a hard time finishing deadlines on time, because you have so much work to do, the type of work we do needs time, you can't rush things. We need more staff, that's for sure" (KI4)*
Opportunities (external conditions)	**Participants quotes**
Independent authority	*"We are independent from the MOH, so the production of new policies and guidelines doesn't require the MOH approval and the long process of approving policies. Internally at least we can produce our own policies and guidelines and the MOH can't intervene with this" (KI8)*
Working in collaboration with regional and international agencies	*"Cooperation with international authorities is very important, we have several collaborations with agencies for example the WHO, which also have many competent followers, and we are growing along with the global advancements of these followers" (KI2)*
Expand through GCC cooperative efforts	*"Being part of the GCC and during our communications with the GCC countries for central registration, we learn that certain guidelines must exist which will make our life easier" (KI6)*
Threats (external conditions)	**Participants quotes**
Poor funding resulting in lack of significant regulatory procedures	*"We need experts on pharmacovigilance, more staff and connections with referenced countries and hotlines, and more importantly, we need a full team and a guideline to start with, this all needs more money" (KI1)*

Open market	*"When consumers do not find what they need from the market they would easily order HMs online and who knew what these products include they might've contained banned and dangerous substances, these are not tested" (KI5)*
Increased number of substandard and counterfeit HMs	*"Unsafe HMs are incredibly increasing all over the world, many products we received did not meet the required quality or safety, we need to be very careful with herbs and very thorough in our review" (KI4)*

GCC Gulf Cooperation Council, *HMs* herbal medicines, *HPs* health products, *MOH* Ministry of Health, *SOPs* Standard Operating Procedures, *WHO* World Health Organisation

Additional file 6.6: Data from the analysis of interview transcripts on Strengths, Weaknesses, Opportunities and Threats of the current HMs registration system at the Bahraini drug regulatory authority

Additional file 6.7: An analysis of the registration process of HMs at the Herbal Department, Dietary Supplement Department and Unclassified Department in the Kuwaiti drug regulatory authority, including similarities and differences between the three departments

(A) Submission

The Kuwait Drug and Food Control and Administration (KDFCA) does not have a system for appointments, product's dossier is submitted directly to the Director of the KDFCA with an official request letter from the local agent to register the product in the specified department, where the Director officially accepts the dossier and transfers it to the Drug and Registration Release Superintendent (DRRS) who transfers the dossier to the requested Department. The validation of the dossier begins in the same day as receiving whereby the reviewer verifies submitted administrative, quality, safety and efficacy requirements. Requirements for HMs in the Dietary Supplement and Unclassified Departments are less demanding than requirements in the Herbal Department (**Table 6.1**).

Table 6.1 Summary comparison of key registration requirements of HMs in each department extracted from Herbal Department Ministerial Decree (201/97), Dietary Supplement Department Ministerial Decree (532/2002) and Unclassified Department Ministerial Decree (201/99)

Regulatory requirements	Herbal Department	Dietary Supplement Department	Unclassified Department
Administrative			
Application form completed by the agent	✓	X	X
Checklist completed and signed by the manufacturer	✓	X	X
Finished product sample and leaflet	✓	✓	✓
Original Legalised Free-Sale Certificate or Certificate of Pharmaceutical Product	✓	✓	✓
Status of registration of the product in the country of origin	✓	✓	✓
List of countries where the product is registered with registration dates and numbers	✓	✓	✓
Original legalised price certificate	✓	✓	X
Quality			
A "Free From" certificate issued by the manufacturer	✓	X	X
Certificate issued by the company stating that the product does not contain or contains the allowed percentage of heavy metals	✓	X	X
Finished product specifications	✓	X	X
Certificate of analysis of finished product	✓	✓	✓
Complete stability study on three production batches	✓	X	X
Raw materials (both active substances and excipients) specifications and certificate of analysis and certificate of suitability of the active ingredients	✓	X	X
Original legalised pork free/ alcohol free certificate	✓	✓	✓
Safety			
Safety studies from approved international authority or scientific references	✓	X	✓
Efficacy			
Clinical studies/ scientific references	✓	X	X

(B) Evaluation

In all three departments, scientific assessment and laboratory analysis both proceed in parallel. For the scientific assessment, reviewers start the assessment process by verifying the submitted documents and making sure that they are in a clear and unambiguous order within the file. In all three departments reviewers perform an 'abridged' review for assessing the documents submitted concentrating on assessing submitted quality data in relation to climatic conditions, finished product specifications and Certificate of Analysis to ensure that the quality data submitted are within the specifications. Other data are not investigated unless a query is raised on a specific product. An assessment template is used by reviewers in each department to provide a standardised content and format of the data assessed to present a scientific study report.

Not all HMs in the three departments undergoes the analysis because the authority relies on the Certificate of Analysis submitted by the agent from the manufacturer. However, all sexual and slimming herbal products must pass the testing to check for adulteration of products with other substances such as Sebutramine or Sildenafil. After the analysis is complete, the analysists prepare a quality assessment report stating whether the product has passed or failed the analysis. The report is then transferred to the concerned registration department where the reviewer completes the scientific study report.

Questions are collected as they arise during the scientific assessment and laboratory testing and are provided to the agent. Unlike the Herbal Department, the Unclassified and Dietary Supplement Departments does not place any limits on the agent's response time. In all three departments, once the response from the company is received, it is reviewed by the same appointed reviewer who initially reviewed the registration dossier, and accordingly a final decision is taken.

(C) Authorisation

In all three departments the scientific reviewer proposes the final approval decision individually which is signed off by the Head of each department and the DRRS.

Products registered at the Unclassified Department do not enter the pricing stage and are priced according to the company's desires. For products in the other two departments a pricing committee

consisting of the Head of the Pricing Department and at least two reviewers decide on the price which is usually the export price to the Saudi market.

Once the product is approved (for HMs in the Unclassified) and priced (for HMs in the Herbal and Dietary Supplement Departments) the local agent is provided a first release to order the first shipment of their registered product. For HMs in the Dietary Supplement and Unclassified Departments, the agent submits the shipment invoice to the reviewer to grant the second release and the products can be released into the market. For HMs in the Herbal Department, in addition to the submission of the shipment invoice, the agent is required to submit a sample from the shipment to the laboratory for analysis to check for any heavy metals and microbial contamination. The test results are sent back to the same appointed reviewer who provides the second release and the product can then be released into the market.

Additional file 6.7: Data from the analysis of fieldnotes and documents on the registration process of HMs in the Herbal Department, Unclassified Department and Dietary Supplement Department at the Kuwaiti drug regulatory authority

Additional file 6.8: An analysis of factors affecting the Kuwaiti drug regulatory authority's readiness to implement the proposed recommendations

Table 6.1 Contextual factors affecting the Kuwaiti drug regulatory authority's readiness to implement the proposed recommendations, with participants' quotes

Contextual factors		Participants quotes
Policies and procedures	Reviewers suggesting that current management must be changed	*"The authority needs young minds, people who are motivated to improve the place. Giving someone a high position comes with responsibilities and improving the system is one of them. When this person has reached a very advanced age, they do the minimum, and do not really care whether this place needs new regulations or guidelines, they are not bothered to make progress, and the place goes back in time and becomes underdeveloped. Renewing the blood, improves systems" (KI10)*
	Increase motivation in improving the system through rewards and promotions	*"It is the nature of our work you know, we do not receive rewards and bonuses when we succeed in improving the system or when we work really hard, we get promoted because of the years we serve, so the staff is not motivated to improve the system, they will gain nothing from that"(KI11)*
	Increase the interaction between management and reviewers	*"They [management] need to know the issues and be ready to hear the proposed solutions. Management are not working on their own, we are under them and we carry most of the critical procedures, we actually do all the work, if we don't share what views we have with them, how would they know? At the end, we all work together here, at the same place, and the reputation of this place touches us all. It is the managements' benefit to support us" (KI11)*
	Management willingness to involve whoever is necessary	*"There should be direct involvement between us [managers] and reviewers in policymaking and implementation, because I believe that this can contribute positively on the policy and we [managers] can gain from their [reviewers] experience. There is no denial in this. We are willing to involve any employee we could benefit from" (KI14)*
	Approving the policy as a Ministerial Decree	*"High ranking approval. I can prepare a guideline, train people, have it ready, but if you don't have the support of the high ranking, and get it approved, either as an administrative or they send it to the Ministry, to get it approved as a Ministerial Decree, basically you're standing still" (KI20)*
	Separate the KDFCA from the MOH	*"The best thing about it [KDFCA independency from MOH] will be how quick to introduce and implement any new legislation. And it's the easiness of improving and updating, without the formalities of the Ministry. And it gives an extra strength to the power of the administration to have overall control over anything related to medicine. This is the trend worldwide to have the medicine agency separate from the Ministry" (KI20)*
Past experience	The policy should be compatible with other countries	*"We do not want to have our own guidelines that cannot be implemented because it is very different than the guidelines of the countries we are importing from you know" (KI11)*
	Must take into account the exporting countries' classifications when preparing the policy	*"…the documents that the agent will be able to provide depends on how the country [exported country] classify this product. The guideline that you will be implementing, it will cause problems if it is not aligned with international classifications and will be hard to implement in practice. If you think about the main problem, it is the differences in classifications that the different countries around the world have. This cause the problems and companies take advantage of this" (KI23)*
	Continuous update of the policy and discussions with employees to discuss any issues	*"We must not make the same mistake as with ministerial decrees that are now very old because they were not updated. With the guideline, we will have to review the guideline and check for updates in other international guidelines and see if our guideline would need reviewing as well" (KI10)*
	Providing an adaptation period for agents	*"We can give them [agents] like a period of time to adapt themselves to the new routine" (KI9)*

Organisational resources	Increase staff and employ specialists	*"We will need more crew. Re-classifications mean new registrations. You are asking the agent to provide with all required documents like a new file and will need to register it all over again according to our (herbal unit) registration requirements" (KI9)* *"Not every pharmacist is familiar with all the herbs so the specialist is very important especially in the terms used for herbs and medicinal plants. You will have guidelines, so that is fine, but when someone argues on why you are implementing this thing, the specialist will need to explain it to the agents. That is why it is important to have specialists who truly understand why the guidelines are being implemented" (KI23)*
	Apply training	*"You have updates every now and then, almost in the year you have more than one update, every reviewer is entitled to know about these updates, the changes that are happening, and why they're happening, and how to implement them, because they are happening and we're not isolated from the world. We need to be in line with international guidelines" (KI20)*
	Sufficient financial resources	*"The Ministry of Health holds an enormous amount of budget and it doesn't have strategic plans and a specific system for budgeting, it finance all departments under it freely, financial resources won't be a problem here" (KI21)*
Organisational culture	To limit mediation and favouritism more than one reviewer decides the classification or establishing a separate unit for classification	*"See, it is very hard to have a professional relation with people you are already friends with. It is just the way it is. Call it social connection or cultural bond… That's why I said it needs to be away from the agents…Mediation and making favours, can never work on a group, it works individually secretively between two people, so what we can do is that more than one reviewer decides the classification of the product not only one. To double-check it. If it is a group, then it will be managed correctly" (KI12)*
	A separate office or a reception that welcomes the agents	*"we don't have a private room when agent give us files, and discuss issues, everything is discussed here in front of other reviewers and other agents, and other people here can't concentrate with the work they are doing" (KI14)*
Organisational structure	No change in the structure if only a policy is implemented	*"I don't think that the structure will be affected at all. The guideline should be used by all departments, and whenever a HM is detected in the Dietary Supplement or Unclassified Departments, the reviewer must transfer it to the Herbal Department to get classified and registered properly" (KI13)*
	Change in the structure if a Classification Department is implemented	*"…we are receiving many products that are difficult to classify so I think it will be necessary in the future that we establish a Classification Department to deal only with the classification of products" (KI23)*

HMs herbal medicines, *KDFCA* Kuwait Drug and Food Control and Administration, *MOH* Ministry of Health

Additional file 6.8: Data from the analysis of interview transcripts on the five contextual factors affecting the Kuwaiti drug regulatory authority's readiness to implement the proposed recommendations

Appendix 6.1: Translated Arabic quotes from interviews used in the study

Arabic Quote	English Translation
"لأننا نحاول ناخذ شهادة الأيزو، وعشان ناخذها، كل المستندات، و الأوراق الإرشادية ضروري تتجدد كل أربع سنوات. حتى لو ماكان في ضرورة للتغير، على الأقل التاريخ بالمستند او الأوراق لازم يتجدد" (KI8)	*"As we are trying to achieve the ISO certification, to achieve this certificate, all documentations, guidelines must be revised every four years. If there are no amendments needed, at least the date of the version must be updated" (KI8)*
"عشان نوفر الوقت و الجهد، قلنا نتبنى قوانين و إرشادات دولة نثق فيها، ونتبنى تصنيفها للأعشاب. ليش لازم نسوي عمل مكرر ؟ المفروض مانسوّي أي شي من الصفر، خلينا نجرب نغيّر شغلات يلّي توالم دولتنا و نتبنّى الباجي" (KI8)	*"To save time and effort, we said let's adopt the policies and guidelines of a country that we trust and we adopt their herbs classifications. Why do we have to do a duplicate work? We should not do something from scratch, just try and amend things that suit our country and adopt the rest" (KI8)*
"الشيء المحزن إنّه قوة الشركات و الوكلاء تضاهي قوتنا، إحنا السلطة المشرفة، احنا ألّي مفروض تكون عندنا القوة" (KI17)	*"The sad thing that the power of agents and companies exceeds our power. We are the supervisory authority, we should have the power" (KI17)*
"متطلباتنا بالأعشاب [في قسم الأعشاب] ممتازة، متطلبات قوية جداً، تقريبا تشابهه متطلبات تسجيل الأدوية، فإذا كل أدوية الأعشاب تتسجل هنا، هالشيء راح يأكد إنّه الأثار الجانبية راح تكون اقل ظهور وهذا يزيد من سلامة المستهلكين" (KI11)	*"Our requirements for herbals [in the Herbal Department] are excellent very strong requirements, almost similar to the pharmaceutical registration requirements so if all HMs are registered here this will make sure that side effects are less to appear and this will increase the safety of consumers" (KI11)*
"خبرتنا بالكيمياء والأدوية العادية أكبر من الأعشاب. تأسيس تصنيف أو حتى قوانين تضبط الأعشاب بغاية الصعوبة؛ الموضوع مو بس أسود و أبيض، الموضوع معقّد و إحنا ماعندنا الخبرة. للأسف، ماتدربنا على أسس إتخاذ القرارات. كل شي إعتمد على اجتهادنا الشخصي وقراءتنا و سؤالنا خبراء ثانين" (KI3)	*"Our experience in Chemistry and conventional medicines is more than herbals. Establishing classification or even policies to regulate herbs is extremely difficult; the topic is not just black and white, it is a complicated subject and we don't have the expertise. Unfortunately, we didn't receive training on decision-making techniques. It all depended on our personal effort and reading and asking other experts" (KI3)*
"هذي طبيعة عملنا عرفتي، إحنا مانستلم مكافآت وعلاوات لما ننجح بتطوير السيستم، او لما نشتغل من جد، احنا نترقى من سنوات الخبرة، فالموظفين مو متحفزين يعدلون بالسيستم، ماراح يستفيدون من هالشي" (KI11)	*"It is the nature of our work you know, we do not receive rewards and bonuses when we succeed in improving the system or when we work really hard, we get promoted because of the years we serve, so the staff is not motivated to improve the system, they will gain nothing from that"(KI11)*
"تجديد الدم، يحسّن السيستم" (KI10)	*"Renewing the blood, improves systems"(KI10)*
"شوفي، مشكلتنا الوحيدة اهي مع قسم الأنكلاسيفايد، مو واضحين. هالقسم مو منطقي" (KI16)	*"Look, our only problem is with the unclassified department. They are not clear. This department is not logical" (KI16)*
"الواسطات والمصالح عمرها ماتمشي بمجوعة، تمشي بس بين شخصين أثنين، فشنو نقدر نسوي، انه اكثر من مقيّم يقرر تصنيف المستحضر، مو بس واحد" (KI12)	*"Mediation and making favours, can never work on a group, it works individually secretively between two people, so what we can do is that more than one reviewer decides the classification of the product not only one" (KI12)*

HMs Herbal Medicines, *ISO* International Organisation for Standardisation

Appendix 6.2: Proposed policy recommendations of a definition and a classification procedure for the registration of imported HMs in the Kuwaiti drug regulatory authority

1. Definition: A reasonable anticipated step would be the possibility for Kuwait to adopt a universal harmonised definition of what constitute a herbal medicine for the purpose of registration that would guide the product into the most appropriate conformity assessment. A proposed definition could be:

"Herbal preparations made from one or more herbs as the active ingredients, which may additionally contain excipients, however finished products to which the active substances has been chemically altered or added, including synthetic compounds and/or isolated constituents from herbal material, are not considered herbal. Herbal preparations are intended for prophylactic, therapeutic, or other human health benefits" (WHO, 2000).

In addition to adopting a universal definition for HMs, in order to prevent HMs from being categorised as dietary supplements, which as a result circumvent detailed assessment procedures, a directive should also be specified that **all herbal preparations that match the proposed definition must be assessed under the Herbal Department.**

2. Registration pathways: It is proposed that under the above definition, HMs could be divided into two registration pathways; a) Traditional Herbal Registration (THR) (simplified pathway) and b) Herbal Medicine Registration (HMR) (standard pathway). The THR is to create a simplified registration procedure for all traditional HMs not fulfilling the requirements for the HMR pathway. The main registration requirements for the THR and HMR would therefore be as follows:

Main registration requirements	THR (simplified registration)	HMR (standard registration)
Evidence of quality	GMP standards and QC tests	GMP standards and QC tests
Evidence of safety	Evidence of safe traditional use from published scientific literature or international monographs	Toxicological studies
Evidence of efficacy	Evidence of demonstrated traditional use from published scientific literature or international monographs	Clinical studies

GMP Good Manufacturing Practice, *QC* Quality Control

3. Classifications: In order for a HM to be assessed and evaluated under the appropriate registration pathway, HMs are proposed to be classified according to two key features or characteristics; the presentation of the product and the purpose for which it is administered:

- Presentation: - If a claim to treat a major health condition is added, the product is classified under the HMR pathway. (Include list of conditions for which products are unlikely to get registered at the THR)

  - For a product to be classified under the THR pathway only claims that are functional, structural, or therapeutic indications based on long-standing use are allowed. (Include examples of indications likely to be permitted in THR). Products that include claims of treating, diagnosing, preventing or curing of diseases are automatically classified under the HMR.

  - Products under the THR pathway can only be presented as oral, external and inhalation preparation. Products under the HMR pathway may include any preparation type.

- Purpose: If a product requires the supervision of a medical practitioner, or a medical prescription, the product will be classified under the HMR pathway irrespective of the proposed indications.

7. Chapter Seven: General Discussion, Proposed Recommendations and Concluding Remarks

This chapter draws the programme of research to a conclusion. First, it summarises the key findings from each study in this thesis and illustrates how these address the thesis' overall aim. A description of the proposed herbal medicine classification policy and appropriate roadmap for implementing it in Kuwait is then proposed as a journal format paper which has been submitted as a commentary for publication in the Journal of Pharmaceutical Policy and Practice. Key strengths and limitations of this programme of research are discussed, followed by the implications of the findings on practice. Finally, suggestions for future research are discussed followed by the researcher's personal reflections on the research.

7.1 Summary of Findings

The overall aim of this programme of research was to make recommendations for an appropriate design and implementation of a definition and classification policy, suitable for initial registration of imported, manufactured HMs in Kuwait. The aim was achieved through conducting a series of four studies. The studies began with comparing HM definitions and classification laws in five countries with established HM registration systems, followed by reviewing literature on medicines (including herbals) policy implementation in DRAs. An investigation of the HM classification policy development and implementation in Bahrain, including the current system's strengths and weaknesses, was then performed, and finally an investigation of the Kuwaiti DRA readiness to implement policy recommendations generated from the first and third studies was achieved. To recap, below is a summary of the key and novel research findings, explaining how these findings contributed to addressing the overall aim of the thesis.

7.1.1 Study One: International comparison of five herbal medicine registration systems to inform regulation development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain

By using the five-step policy cycle framework by Anderson [29] to inform this programme of research, and having the first step (identification of the problem) explained in Chapter Two of this thesis, the first study of this thesis addressed the second step of the cycle (formulation of options) by comparing the similarities and differences between the current HM registration systems in five established DRAs. Using documentary analysis by reviewing the regulatory and policy documentation of these countries' DRA websites, definitions, classifications, and main registration requirements in each selected DRA were compared providing a clear international HM classification options. Findings from this study revealed that there is a diversity on how all five DRAs classify HMs for registration, with the UK, Germany, UAE and Bahrain having the highest resemblance in defining and classifying HMs. Under the definition of each of the analysed authorities, HMs are classified into one of two registration pathways. One of the two registration pathways in UK, Germany, UAE and Bahrain offer a reasonable simplified registration for HMs, where instead of full registration as a conventional medicine (i.e. requiring MA and proven clinical efficacy), plausible efficacy as a result of established traditional use is sufficient to prove a product's efficacy. This study further revealed that the US does not offer the traditional use pathway, instead, the HM can be classified as a dietary supplement where products do not undergo assessment in the country's DRA prior to their marketing.

The second pathway in all investigated authorities is to register the HM as any other conventional medicine, which means stricter requirements with regards to evidence of efficacy; requiring evidence of clinical studies. In order for a HM to be assessed under the appropriate registration pathway, this study revealed that all five authorities classify their products according to two key factors; a) the presentation of the product (e.g. preparation type), and b) the purpose for which it is administered (e.g. the nature of medical claims applied, requiring prescription, requiring the intervention of a healthcare professional). This study concluded that in order to ensure that all imported products undergo an appropriate assessment in Kuwait (and other similar imported countries that do not have a clear HM definition in place) adopts a harmonised definition for HM registration, with a directive specifying that every

product matching the proposed definition must be assessed under one department to prevent products of being inappropriately categorised as dietary supplements (especially products that are imported from the US).

7.1.2 Study Two: Medicine policy implementation in drug regulatory authorities: a review of the literature

Having investigated the policy content for HM definition and classification in different countries, and recommending a definition for Kuwait, as part of the second step (formulation of options), the second study in this thesis reviewed implementation experiences of medicines and HMs policies in DRAs using published research evidence. Particularly, this study focused on factors that can act as facilitators and/or barriers to policy implementation (with the exception of countries that rely mainly on medicines donations). Findings from this study revealed that there is absence of empirical research investigating HMs policy implementation in a DRA setting, and the identified research was limited to evidence in medicines policy implementation, mostly conducted in LMICs. Using Anderson's [29] four determinants of policy implementation, this review highlighted a body of facilitators and barriers related to political, resources and actors, with little emphasis on the cultural determinants acting only as barriers. Key facilitators from this study involved the efforts of countries in harmonising policies with neighbouring countries with political ties, the involvement of researchers in the decision-making process, and effective communication between staff and management. Key barriers involved the lengthy process of approving policies, lack of training for implementers, lack of management involvement in the implementation process, and lack of managers' appreciation towards staff. However, using criteria to assess the quality of included papers, the assessment showed that the majority of papers had several methodological weaknesses including limitation in data collection and analysis, limitation in the illustration of findings and lack in the use of theories and frameworks to guide interpretation of findings. This study concluded that there is a need for high quality and context specific research to better understand factors that affect medicine policy implementation success or failure.

7.1.3 Study Three and Four: A qualitative exploration of Bahrain and Kuwait herbal medicine registration systems: policy implementation and readiness to change

Owing to the absence in empirical evidence that investigate specific HMs implementation experiences in literature, lack of evidence in organisational culture and its influence on its members, and the poor quality of papers investigating medicines policy implementation experiences, the third (stating content) and fourth (implementation) steps of the policy cycle consisted of two qualitative mixed-methods studies (Study Three and Four), each adopting a theory or a framework to guide interpretation of findings.

7.1.3.1 Study Three

In Study Three, using Walt and Gilson [97] policy analysis triangle, the policy development and implementation process in Bahrain (an established registration system that imports HMs) was investigated to generate insights to inform recommendations of a suitable HM classification system for Kuwait.

Findings from interviews and documents revealed that the development of the policy was based on producing a binding classification guideline through committee meetings using research and informed evidence from DRAs with established HMs systems, and involving all HMs staff and management, with the assistance of external HM regulation experts. Findings from interviews with reviewers and managers revealed that key facilitators that resulted in a successful development and implementation of the policy involved having access to HMs classification laws of well-established DRAs, cooperation and dedication of all officials, the continuous support and efficiency of the government in finalising the policy, strong leadership among management to guide and support reviewers, harmonising the classification policy with policies of countries that Bahrain mostly imports from, involvement of the implementers (reviewers) and external experts in the production of the policy, and enforcing punishment laws to anyone who violates the content of the policy. Key barriers were the diversity in how export countries classify and regulate HMs, lack in providing an implementation plan which resulted in neglecting the allocation of sufficient financial and human resources causing lack in training and high staff

workload, lack in reviewers experienced in HMs, and agents' resistance to comply with the new policy.

Findings from a SWOT analysis of the current HM registration system, revealed that the most commonly identified strengths of the system were availability of guidelines and standard operating procedures which are continuously updated, the Bahraini DRA being perceived as a well-established DRA by neighbouring countries, and implementing an electronic review system assessing HMs requirements and documentations which in turn minimises errors. Major perceived weaknesses of the system include a lack in communication between different departments in the authority because of an unsophisticated organisational structure, and the inappropriate management of financial resources resulting in unequal training opportunities across the authority's departments. Opportunities in the current system were the independence of the authority from the MOH which gives the DRA the autonomy to produce and manage policies. The privilege of Bahrain being a Gulf country is the ability of the DRA to share with other Gulf countries through knowledge transfer. In terms of threats on the current systems, interviewees perceived these as the industrial growth of dangerous adulterated HMs, absence of an adverse effects reporting system and the importation from countries with weak HMs regulations.

Findings from observations revealed that the HM registration process in Bahrain was found to be clear, organised and in line with the classification policy, dividing the HM process into a simplified registration (as a herbal product where plausible efficacy based on traditional use is sufficient to prove the product's efficacy) and a stringent registration system (as a herbal medicine requiring evidence of clinical studies to prove the product's efficacy).

7.1.3.1 Study Four

Using insights into the HM registration system in Bahrain, and findings from the five-country comparison study (Study One), policy recommendations for Kuwait were formulated which consisted of adopting a clear harmonised definition of what constitute HMs for registration, and to introduce a Traditional Herbal Registration based on this definition and the product's characteristics. These recommendations were used in the fourth and final study of this thesis which explored the staff and the authority's readiness for implementing the proposed policy recommendations. Before

this, observations of the current HM registration process revealed that under the current system, other than the Herbal Department, HMs are being registered in two other departments that are also concerned with registering dietary supplements, functional food and medical devices. Findings from observations and documents revealed that HMs in the two other departments lack rigorous assessment and laboratory analysis prior to their marketing and one of them does not require pricing by the authority.

Findings from interviews about participants' concerns of the current system revealed that reviewers are confused on how to register HMs, including herbal products that also contain vitamins and minerals. The agents and manufacturing companies seize this confusion to register HMs in certain departments for the purpose of increasing their profits. Findings from interviewees' opinions about the proposed recommendations revealed that almost all reviewers and managers were in favour of the proposed recommendations and were enthusiastic to implement them. Interviewees also shared several benefits of implementing such recommendations, such as having a consistent HM registration process, increasing consumers' safety through appropriate pre-marketing assessment, and increasing reviewers' decisiveness in making classification decisions.

Using TORC contextual factors, interviewees identified potential challenges which may impede successful implementation such as the Kuwaiti DRA being structurally and administratively under the MOH which is causing difficulties for the Kuwaiti DRA to improve its regulations, the extreme shortage in reviewers, resistance of pharmaceutical companies to changes and the impact of cultural and traditional ways of working which affects some important regulatory decisions such as the management exercising favouritism with certain agents.

Overall, evidence into how other countries define and classify HMs (five-country comparison study), and insights into policy development and implementation experiences in a well-established system (Bahrain); in addition to the exploration of Kuwait's readiness for implementation, facilitated final policy recommendations and implementation plan for Kuwait which was written-up as a commentary paper in the following section (Section 7.2).

7.2 Proposed Herbal Medicine Classification Policy and Implementation plan

Title	Herbal medicine classification: policy recommendations and implementation roadmap
Type	Commentary
Authors	Alostad AH, Steinke DT, Schafheutle EI
Submission date	22 September 2019
Status	Under review *
Journal	Frontiers in Medicines

*Note. As this paper is currently under review, the formatting and layout are consistent with the journal's guidance. References from the paper are placed at the end of the chapter rather than at the end of the thesis.

Herbal Medicine Classification: Policy Recommendations and Implementation Roadmap

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Abstract

Countries which import herbal medicines (HMs) from other countries and assess these HMs in light of the regulatory status in their country of origin face inconsistency in the registration process in their drug regulatory authority's (DRA) structure. Some products may be classified as a product requiring limited assessment for quality, safety and efficacy in their country of origin and thus escape rigorous assessment in the destination country, raising potential safety concerns for consumers. Kuwait is a country which imports all of its HMs and lacks a clear definition and classification policy for the registration of imported HMs in its DRA structure. In order to inform a HM classification policy for Kuwait, a review of existing evidence, a comparison of select other countries' systems, and empirical research in a country with an established HM system was conducted; a readiness for change study was also undertaken in the target country Kuwait. The findings from these studies informed recommendations for a suitable classification policy and implementation plan. This commentary provides a description of the proposed policy which consists of adopting a clear definition for HM registration and implementing the Traditional Herbal Registration concept based on specific product characteristics. A roadmap for implementation in Kuwait is proposed which involves adopting a clear classification and enforcing it with a decree, involving employees in the detailed development and implementation process, allocating required financial and human resources prior to implementation, and the possibility of the Kuwaiti DRA to obtain independence from the Ministry of Health. To promote universal harmonisation, the proposed policy and implementation plan can inform policy implementation in other countries.

7.2.1 Background

Herbal medicines (HMs) have been defined as "preparations manufactured industrially consisting of active ingredient(s) which is/are purely and naturally original, not chemically altered plant substance(s), and is/are responsible for the overall therapeutic effect of the product" [1]. Due to a belief that as 'natural' products, HMs are 'safe' or 'safer' than conventional medicines, consumers have turned to plant-derived preparations [2]. However, similar to conventional medicines, HMs contain several chemical constituents, that are capable of producing pharmacological effects causing both mild and serious adverse effects, ranging from renal disfunction, liver toxicity, elevated blood pressure and even death [3, 4]. Safety issues of HMs may also arise when the product is contaminated with bacteria, yeast or mold, or is adulterated with orthodox medicines [4, 5].

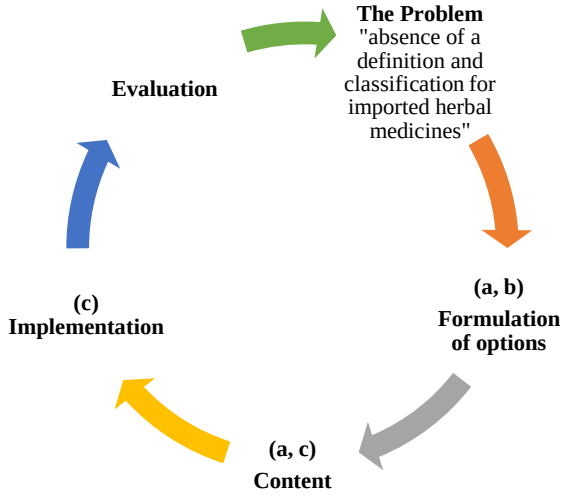
The pre-marketing control of medicines in drug regulatory authorities (DRAs) helps to assure the safe use of all medicines, by performing appropriate quality, safety and efficacy assessments prior to their marketing [6]. To do so, DRAs require manufacturing companies to submit evidence of adherence to Good Manufacturing Practice (GMP) and quality control to demonstrate the product's quality, and evidence of toxicity screening to prove the product's safety. The research protocols, standards and methods required for the evaluation of HMs' efficacy are more complex and difficult to obtain [7]. Unlike conventional medicines, a single HM may contain hundreds of natural constituents, and a mixed HM may contain several times more that number. This poses standardisation, ethical and financial strains to perform clinical trials for HMs, limiting the ability of manufacturing companies to fulfil the requirement of clinical efficacy [8].

The occurrence of high-profile safety concerns of HMs, coupled with the difficulty to demonstrate clinical efficacy, mandated that DRAs have regulatory evaluation measures in place to ensure the safe use and availability of HMs in their market [9]. However, in some countries, HMs are not regarded as medicines but as foods or dietary supplements, as such requiring less rigorous regulatory assessment than medicines [3] This global regulatory inconsistency on how countries define and classify HMs has an effect on small countries such as Kuwait, which lacks the capacity to manufacture its own HMs, and therefore imports all of its HMs from other countries. The issue in the Kuwaiti DRA structure is that a clear classification and definition of

what is considered a HM for registration does not exist. Therefore, the classification of the product in the country of origin guides how the product is dealt with prior to marketing. This causes inconsistency in how products are assessed in the Kuwaiti DRA, with some HMs being assessed in the Herbal Department but others in other departments with less stringent requirements [3]. In order to allow a standardised approach for evaluating the quality, safety and efficacy of imported HMs into Kuwait, and ensure public safety, it is essential to develop a clear HM definition and classification procedure in the Kuwaiti DRA structure and make recommendations for its implementation [10].

To inform such a proposal, the authors conducted a four step research study using Anderson's policy framework (**Figure 7.1**) which emphasises using reliable evidence to inform future policy design and implementation [11].

Figure 7.1 Description of research conducted within the policymaking cycle adopted from Anderson [12]



(a) Study One: country comparison of five advanced herbal medicines registration systems: Germany, United Kingdom, United States, Kingdom of Bahrain and United Arab Emirates [1]
(b) Study Two: review of published literature investigating facilitators and barriers influencing medicines (including herbals) policy implementation in drug regulatory authorities [12]
(c) Study Three and Four: examination of the policy development and implementation process in an established herbal medicine registration system (Bahrain), and exploration of policy implementation readiness in the Kuwaiti drug regulatory authority [13]

The first study consisted of a comparison of five established HMs registration systems that are either exporters of HMs into Kuwait (Germany, United Kingdom (UK), United States (US)), or countries that are culturally, financially and geographically similar to Kuwait (Bahrain and United Arab Emirates (UAE)) [1]. The second study consisted of a review of relevant implementation literature [12]. The third and fourth studies consisted of a qualitative exploration of an established system (Bahrain), which similarly to Kuwait, relies on registering HMs manufactured elsewhere, followed by an investigation of Kuwait's system and readiness for implementation [13]. Using the findings from the above studies, the aim of this commentary is to provide a description and justification of the proposed definition, classification policy and the plan to implement it, generated from the four studies.

7.2.2 The recommendations

7.2.2.1 Proposed definition and classification

Findings from comparing the HM registration laws in five countries [1] revealed that all comparative authorities state in their HMs definitions that the product must consist of plant materials, with Germany, UK (under European Union Directive 2004/24/EC), Bahrain and UAE having the highest similarity in defining a HM. These four countries' definitions are consistent with the recommended World Health Organisation (WHO) definition of an "authorised industrially manufactured therapeutic herbal product for registration" [14]. To promote international harmonisation, the WHO definition (**Figure 7.2**) can be considered for Kuwait, which has already been adopted and adapted in many countries including importing countries in Africa [15] and the Middle-East [16, 17].

The five-country comparison study [1] also showed that the US market HMs as "dietary supplements", which does not require any pre-marketing evaluation. In the US, the regulation for dietary supplements is a reactive rather than proactive approach, whereby these products can be placed in the market with no quality, safety or efficacy evaluation unless a safety incident has occurred or a case can be made that a particular product poses a specific danger to the public [3]. Evidence already exists that classification of HMs as dietary supplements has resulted in serious and growing public health problems [18].

Figure 7.2 Preview of the proposed herbal medicine classification policy

Definition

"Herbal preparations made from one or more herbs as the active ingredients, which may additionally contain excipients, however finished products to which the active substances has been chemically altered or added, including synthetic compounds and/or isolated constituents from herbal material, are not considered herbal. Herbal preparations are intended for prophylactic, therapeutic, or other human health benefits" [14].

Registration pathways

Under the above proposed definition, HMs could be registered under two registration pathways; a) THR b) HMR. The THR is to provide a simplified registration option for traditional HMs not fulfilling the requirements for the HMR pathway. The main registration requirements for the THR and HMR would therefore be as follows:

Main registration requirements	**THR (simplified registration)**	**HMR (standard registration)**
Evidence of quality	GMP standards and QC tests	GMP standards and QC tests
Evidence of safety	Evidence of safe traditional use from published scientific literature or international monographs	Toxicological studies
Evidence of efficacy	Evidence of demonstrated traditional use from published scientific literature or international monographs	Clinical studies

Classifications

In order for a HM to be assessed and evaluated under the appropriate registration pathway, HMs are proposed to be classified according to two key features or characteristics; the presentation of the product and the purpose for which it is administered:

Presentation: - If a claim to treat a major health condition is added, the product is classified under the HMR pathway. (Include list of conditions for which products are unlikely to get registered at the THR)

- For a product to be classified under the THR pathway only claims that are functional, structural, or therapeutic indications based on long-standing use are allowed. (Include examples of indications likely to be permitted in THR). Products that include claims of treating, diagnosing, preventing or curing of diseases are automatically classified under the HMR.

- Products under the THR pathway can only be presented as oral, external and inhalation preparation. Products under the HMR pathway may include any preparation type.

Purpose: - If a product requires the supervision of a medical practitioner, or a medical prescription, the product will be classified under the HMR pathway irrespective of the proposed indications.

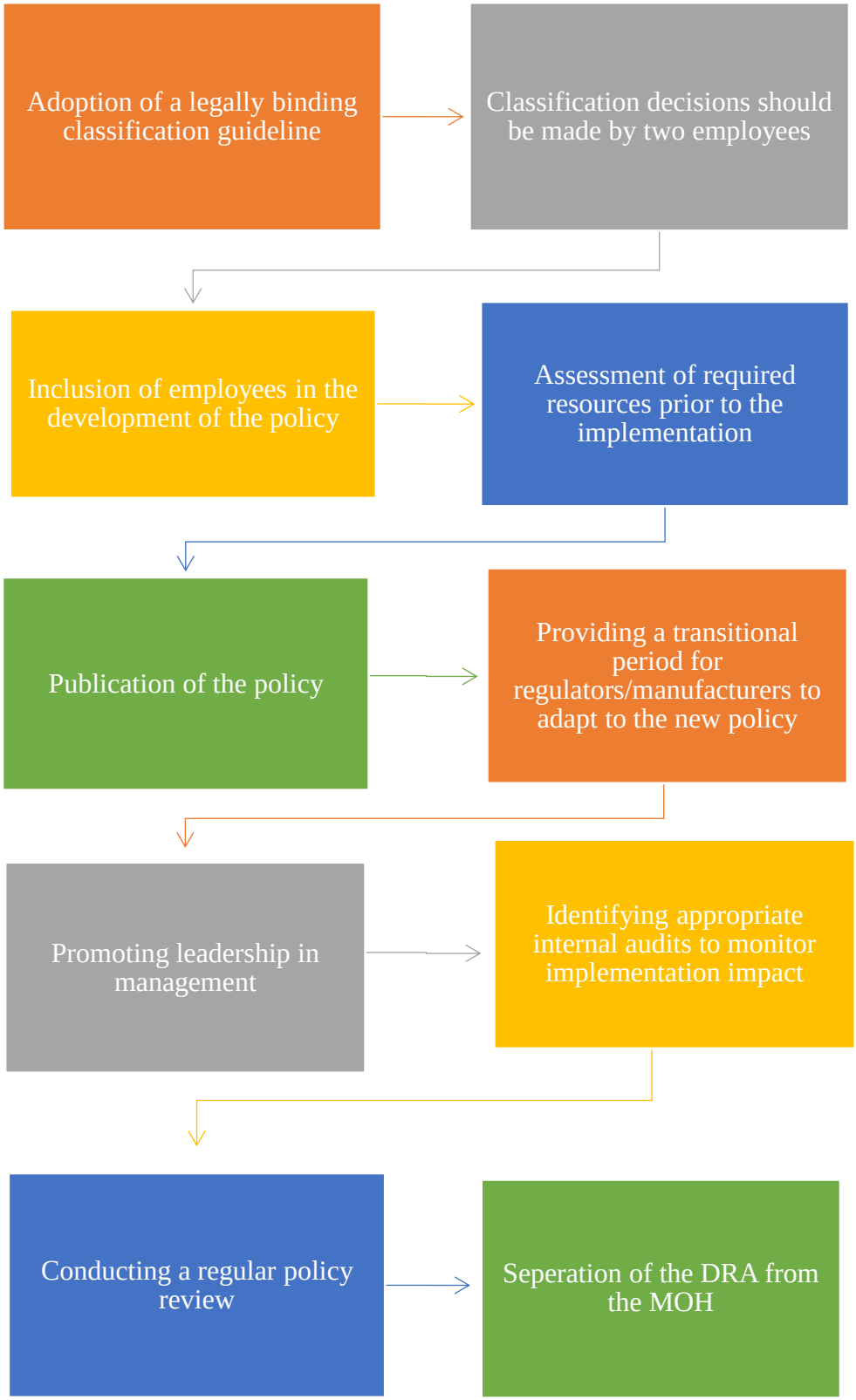
GMP Good Manufacturing Practice, *HMs* herbal medicine, *HMR* Herbal Medicine Registration, *QC* quality control, *THR* Traditional Herbal Registration

A safer and more considered approach in registering HMs was revealed in the UK, Germany, UAE and Bahrain, which all offer a simplified registration called the "traditional herbal registration (THR)" based on the product's presentation and purpose (**Figure 7.2**). In line with the THR scheme, in addition to performing quality and safety checks, 'plausible efficacy' based on evidence of long-standing use and experience is sufficient to prove the product's efficacy. A study that evaluated the impact of the THR scheme in the UK prior to and after its implementation revealed that an increase in the quality of information provided with HMs was achieved [19]. As the THR scheme is associated with appropriate pre-marketing evaluation, and more complete information than the dietary supplements classification, it is proposed that in addition to the choice of applying for a product licence of the type needed to manufacture "conventional" products and providing evidence of clinical efficacy, the THR scheme should be implemented in the Kuwaiti DRA (**Figure 7.2**).

7.2.2.2 Proposed implementation plan

Having recommended a definition and classification policy for the Kuwaiti DRA, it is essential to inform how these recommendations are to be implemented. In exploring the HM classification policy implementation process in Bahrain (including implementation facilitators and barriers) and implementation readiness in Kuwait [13], ten recommendations are proposed to strategically plan potential implementation (**Figure 7.3**). These recommendations are consistent with the medicine policy implementation literature [12], which emphasises the importance of management support and leadership, employees' involvement in the policymaking process, promoting a culture of appreciation and teamwork, and allocation of human, financial and technical resources.

Figure 7.3 Suggested "roadmap" for implementing a herbal medicine classification policy in the Kuwaiti drug regulatory authority



DRA drug regulatory authority, *HM* herbal medicine, *MOH* Ministry of Health

The recommendations are as follows:

1. Adoption of a legally binding HM definition and classification guideline, with an additional route of evaluation and registration for HMs which are not classified as complete medicines (e.g. the Bahraini Pharmaceutical Classification Guideline [13]). Furthermore, to avoid inconsistency in the review process, HMs matching the proposed definition must be assessed in one department (the Herbal Department).
2. To ensure independence and compliance, classification decisions should be made by two employees, with wider discussion where discrepancies are encountered.
3. To achieve good employee buy-in, understanding and adoption, management should involve them in detailed development and implementation of the policy.
4. Resource needs must be assessed prior to policy implementation, including: a) financial resources; laboratory instruments for analysing HMs, employee salaries, costs of training etc. b) human resources; sufficient experienced staff with good knowledge about HMs c) specialised training in HMs and continuing professional development for employees d) access to international HMs references such as the Herbal Medicines Compendium, European Pharmacopoeia, Japanese Pharmacopoeia and British Pharmacopoeia.
5. When the final policy has been approved, and in the interest of transparency, it should be published on the Kuwaiti DRA official website. Manufacturers should then be informed regarding content and implementation.
6. A transitional period should be given for traditional HMs already on the market, allowing sufficient time for all stakeholders, including manufacturers and agents, to adapt to the new requirements.
7. Promote leadership by identifying advocates that could facilitate and enhance acceptance of the new policy in a positive working environment.
8. Identify appropriate and independent monitoring measures (internal audit) by a separate department to ensure that the employees' performance meets the authority's demands and expectations. The audits can include obtaining employees' and manufacturers' feedback, inspections to monitor classification consistency and compliance through observing employees' performance and tracking of HMs applications.

9. Conduct a review of the policy (e.g. every five years) which could be achieved by considering to engage with external HM regulatory experts to ensure that the policy is updated according to international laws.
10. A future recommendation is the possibility of separating the DRA from the Ministry of Health to become a separate juristic body, thus ensuring decisions are guided by interests of public health and safety, and expediating decisions.

7.2.3 Conclusions

Based on evidence and empirical research, an outline of a policy specifically for HMs classification was generated, in which by implementing it, a registration consistency, and an increasing safety level can be expected. Practical implementation steps were proposed to facilitate the transfer of the new policy. Although the proposed policy and implementation roadmap were generated for Kuwait, the policy can be adopted to promote international harmonisation of HMs registration, and the implementation roadmap can be tailored for other countries that do not have such policy implemented.

Ethics approval and consent to participate No ethical approvals were required for writing this commentary.

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7.2.4 References

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7.3 Key Strengths and Limitations of the Studies

This PhD set a broad aim of informing a HM registration policy in Kuwait by exploring how other countries' HMs policies are developed and implemented by employing a systematic theoretical framework [29]. This framework guided the formation of all studies, in which it was possible to generate final recommendations based on evidence from each study (Section 7.2). There are some strengths to the research that was conducted as well as limitations that should be considered when/if adopting the conclusions presented in this thesis. These are discussed below.

7.3.1 Strengths

As there is no consensus of what is defined as an "authorised industrially manufactured therapeutic herbal product for registration" a standard definition based on the current characteristics of products assessed in the Kuwaiti DRA's Herbal Department was used when conducting the research studies. The use of the standard definition allowed better clarity and consistency in this research. Moreover, the use of a standard definition could allow better comparisons of findings with studies conducted in Kuwait and other countries, and could make it easier for researchers to apply their findings both domestically and internationally.

Study Three and Study Four are the first studies to explore, in-depth, the development and implementation process of a HM classification policy and its readiness for implementation. The strengths of these qualitative studies lie in their novel methodological approach in obtaining data using a combination of policy framework and theory that ensured that the analysis and interpretation was grounded in the data. A call for a greater explicit use of frameworks and theories within implementation science has been made by many authors in order to optimise their design, identify conditions of context necessary for their success and enhance learning from those efforts, and to shorten the time needed to develop improved interventions [91, 152 -154]. The application of theory in this thesis helped to strengthen the development of policy recommendations and an implementation plan. Moreover, the two studies utilised three different qualitative data collection methods (observations, documents and interviews) and provided a comprehensive picture of the HM system in both authorities. The impact of using interviews solely, could make the obtained data inaccurate or exaggerated to the benefit of the participants or the explored system.

The normal memory recalls in a reconstructive way that is adapted with current knowledge and beliefs, rather than reproducing the event as it occurred [155]. Therefore, only using interviews to describe the registration and classification process in both authorities could have resulted in recall bias which could have affected the accuracy of events [156]. The use of observations and document review in addition to the interviews helped to produce a real and rich detailed data of the current classification and registration situation in both investigated authorities. Moreover, follow-up interviews allowed to tailor interviews based on the observations and validated the interpretation of fieldnotes and documents.

As explained by Merriam et al. [157], "…being an insider means easy access, the ability to ask more meaningful questions and read non-verbal cues, and most importantly, to be able to project a more truthful, authentic understanding of the culture under study". Indeed, the working history and the nationality of the researcher (being a Kuwaiti employee at the Kuwaiti DRA) was an advantage in Study Three and Study Four. Being from the same culture as that under inquiry has helped the researcher understand clearly the complexity of the situation under investigation and explored the factors in more detail. Being sponsored by the case study organisation (Study Four) has facilitated an abridged approval process for conducting the research, accessing the field and recruiting participants.

7.3.2 Limitations

In Study One, although Kuwait imports HMs from many countries other than Germany, UK and US and is similar in geography and approach to several countries other than Bahrain and UAE, the restricted time and resources during this programme of research allowed only limited number of countries with well-established HMs registration systems to be investigated. In study Two, the review of the literature used only three databases to search for factors that may influence medicine policy implementation in a DRA setting. However, the three used databases are the largest and most trusted medical and social science databases with the highest journal coverage that are rapidly updated [158, 159], and therefore, the likelihood of missing papers that are related to the inclusion criteria of the study would be minimal.

While this is perhaps more a matter of style than substance and possible due to making a policy analysis fit into the rigid Background/Methods/Results/Discussion of Study Three and Study Four, details on for example the budget, workload, and the

nature and frequency of training courses could not be obtained for Bahrain and Kuwait DRAs, as both authorities did not keep records concerning such information.

Despite the 100% participation rate in both studies who targeted all the officials working directly with the registration of HMs in Bahrain and Kuwait DRAs, the main limitation of these studies is the relatively small number of participants. This was reasonable since the limitation of staff was one of the barriers and weaknesses reported in both authorities. However, it has been argued that the objective of qualitative study research is not to draw suggestions about larger population, which is the case with quantitative studies, but rather to generalise back to a theory or application [117]. In this research, each participant from the two studies contributed towards a rich amount of data resulting in data saturation.

Another limitation in Study Three and Four is the use of case study approach. The approach used that was conducted through participants' views, experiences and insights might be difficult to replicate, and might not represent people in general or go beyond the person or the group studied [131]. On the other hand, the qualitative case study approach had significant strengths such as originality, testability and realistic validity [112].

The speciality of the principal researcher could have had some bias during the data analysis as she could be influenced by her background and experience. However, during the interpretation of data, the researcher and the supervisory team made sure that different opinions both positive and negative were presented.

Another limitation of Study Four may be that authoritarian structures could have resulted in participants not being critical of management. However, since the Kuwaiti DRA is under the autonomy of the MOH, the DRA's management does not have the authority to dismiss staff and therefore it was believed that participants were comfortable in providing their views on management without the fear of being judged or fired. Furthermore, it may be possible that participants in Study Four may welcome almost any recommended classification system as there was only single recommendation that was proposed to investigate the organisation and participants' readiness, with no alternatives provided. However, due to the challenges that countries face in implementing HMs regulations because of their heterogeneity, to promote harmonisation, it was found necessary that only the most appropriate recommendation based on reliable evidence be proposed.

Finally, as mentioned in the theoretical overview in (Chapter 3), this research is limited to its findings which focused on the development and implementation of the HM classification policy, and did not carry an in-depth investigation of the impact of the policy (evaluation) in Bahrain, where there is still little evidence about the concrete impact that this policy has brought. If this aspect has been investigated, this might have affected the recommendations that are presented in (Section 7.2).

7.4 Implications for Practice

This research informed recommendations for a suitable classification policy and implementation plan for the registration of imported HMs into Kuwait. The approach taken and the findings generated could benefit researchers, local and international DRAs, policymakers, reviewers and consumers. The following section discusses some of the studies' implications for practice.

7.4.1 Implications for researchers

During the last few years, global efforts were directed towards promoting the use of research evidence in policymaking [160-162]. However, there has been much less attention to how to perform policy analysis, and what research designs, methods or theories best inform policy analysis [133]. This thesis advocated evidence-informed policymaking aiming to ensure that decision making is well-informed by the best available research evidence in a transparent and systematic way [163]. In Study Two it was demonstrated that researchers working within the field of policymaking need to pay particular attention to their findings and provide rich descriptions of the context and implementation strategy to make explicit reasons for success or failure of policies. Study Three and Four have substantially closed the empirical gap in literature (Study Two) by providing novel insights related to the experiences of HM policy and its implementation in a DRA setting. This thesis provided valuable suggestions on ways that researchers can conduct policy research, draw attention to the importance of using relevant theory and framework to underpin analysis, and proposed a number of different theoretical frameworks to help researchers organise and focus their efforts to analyse the policymaking process. The WHO Eastern Mediterranean Regional Office emphasised, in its directions for health research, that the implementation and expansion of research is a fundamental tool for health development and informing

health policy [164]. Therefore, the approach taken in this thesis can be replicated in other national and contexts as an effective strategy for initiating, promoting and strengthening knowledge translation.

7.4.2 Implications for DRAs, policymakers and reviewers

This thesis has resulted in the development of policy recommendations and implementation plan to guide policymakers in Kuwait and other similar countries in their efforts in informing the HM registration system. It is hoped that the findings of this thesis will enable a greater standardisation, clarity and consistency in the registration process of HMs in the Kuwaiti DRA leading to an increased confidence of reviewers in making classification decisions and reduction in duplication efforts as a result of registering a product with the same active ingredients in different departments. The findings may also contribute to similar initiatives in other regions of the world.

Findings from Study One and Three allowed policy recommendations for Kuwait to be generated involving the implementation of the THR classification based on the availability of evidence of long-standing traditional use of HMs to prove the product's efficacy. The nature of the traditional use evidence of HMs in Kuwait could be similar to the nature of evidence that is used for regulating traditional HMs in Bahrain; e.g. European Herbal Substances Community List, European Herbal Substances Community Monographs, European Scientific Cooperative on Phytotherapy (ESCOP) Monographs or published peer-reviewed scientific literature and/or other recognised HM text books establishing the traditional use of the product locally or/and internationally [165].

Findings from Study One showed that each investigated country defines and classifies their HMs differently. As issues relating to adverse reactions are increasing and are no longer debatable, regulatory policies on HMs need to be standardised and strengthened on a global scale. Relevant regulatory authorities need to be proactive and implement appropriate measures to protect public health by ensuring that all HMs approved for sale are safe and of suitable quality. This is particularly essential in the US where HMs are regarded as dietary supplements which can be produced, sold, and marketed without first demonstrating quality, safety or efficacy. The US FDA bears the regulatory burden of proving that a dietary supplement is causing safety issues, before it can be removed from the market [4]. Consequently, this regulatory

classification has led to safety problems of herbal products [166]. A US DRA analysis of several supplements on the US market revealed that in many cases, the supplements did not contain the listed ingredients in the stated amount or at all, and some products were recalled because of contamination with pesticides, microbes, or heavy metals [166]. One investigation of over-the-counter anabolic steroids found that a product contained 77% more testosterone than stated on the label [167]. Moreover, a recent analysis of 25 marketed ginseng products found a significant increase in the concentration of two ingredients believed to have biological activities; ginsenosides and eleuthrosides [168]. In a study that was conducted to explore Americans' views on the regulation of dietary supplements, it was revealed that there was broad public support for increased government regulation of these products [169]. The study found that the majority of Americans surveyed supported that the US DRA review the safety of new dietary supplements prior to their sale, and to increase government regulation to ensure that advertising claims about the health benefits of dietary supplements are accurate. The US DRA therefore should have a proactive role in setting their quality and safety standards to protect the public's health. A certification system for the herbal content and potency of marketed products should be established by the DRA in conjunction with the herbal drug industry. The system could utilise other countries' regulatory experiences (e.g. EU THR scheme). There is now data (from Study Three and Study Four) about the expected benefits of implementing a harmonised HM classification policy, and how to adopt it. If US HMs manufacturers were allowed to apply for traditional usage registration with providing sufficient evidence of traditional use, the US DRA could have a two-tiered regulatory system for HMs, similar to those adopted by other developed countries. Such a system would not only allow consumers to make rational choices about the use of HMs and keeping those products safe, but with the US being one of the largest exporters; covering 35% of the world's dietary supplements market [170], this could also facilitate the safety and harmonisation of HMs regulation globally. Several experts have also suggested a number of other recommendations to the regulation of dietary supplements that could improve the safety and appropriate use of these products in the US [171, 172]. These include: (1) requiring manufacturers to register with the US DRA including performing frequent manufacturer audits which could assist efforts to identify and deal with breaches of GMPs, (2) requiring safety tests similar to those required for over the counter

medications, and (3) ensuring that the labels on all products provide an accurate list of all ingredients.

The use of ineffective, counterfeited, and poor quality HMs can result in therapeutic failure, adverse reactions and sometimes death [173]. The sample analysis stage is a vital step of the review process to ensure that the product is safe and of the desired quality prior to marketing. Findings in Study Four revealed that although samples from shipments of all approved HMs are sent to the QC laboratory for analysis before they are marketed in Kuwait, the collection and supply of the samples is carried out by the applicant. This process may create an uncertainty with regard to the authenticity of the product, as the sample provided may not be identical to the batches released into the market. Therefore, it is important to note that the proposed classification policy would not necessarily reduce the risk of adulterants. An appropriate practice that the authority needs to consider to ensure that samples submitted for analysis are taken from the same batch that is projected for marketing, is to perform batch control [174]. According to this procedure the first batch of a HM, is "put in quarantine" while a random sample is taken by suitable qualified personnel, and analysed by the KDFCA laboratory for confirmation of its quality and safety. The batch can then be released only after a satisfactory result is obtained. To ensure the quality and safety of subsequent batches, the authority can perform random sampling from outlets where HMs are marketed. Such a mechanism would provide ultimate consumer health protection.

Even if pre-marketing evaluation has been thoroughly conducted, it may not be sufficient to assure the safety of drugs [28]. Therefore, to protect the public health from harmful effects of HMs after they are approved for marketing, emphasis should also be placed on establishing a post-marketing surveillance. From Study Three, the SWOT analysis revealed that the Bahraini DRA lack a system for the reporting of adverse drug reactions (ADRs) of medicines; pharmacovigilance system. The need of such a system for Kuwait was also reported in the literature [175]. Although pharmacovigilance is considered novel in Kuwait, some good initiatives facilitating pharmacovigilance activities, such as issuing an online ADRs reporting form to encourage both healthcare professionals and consumers to report ADRs in medicines [176]. However, only a very small number of reports concerning medicines have been received; 212 reports were received in 2016 and 366 reports were received in 2017 [176]. The pharmacovigilance system is a new regulatory system that needs the

appropriate infrastructure, human resources, information technology facilities, educational programmes and quality assurance tools [176]. A guideline has been proposed by the Arab Ministers of Health on good pharmacovigilance practices (GVP) for Arab countries which was adapted from the EU GVP; with the aim to unify all procedures and activities of pharmacovigilance of medicines (including HMs) among Arab countries [177]. Several Arab countries have benefited from the GVP for Arab countries, such as Egypt and Jordan [176]. A sensible step for Bahrain and Kuwait DRAs would be to implement the GVP guidelines. If such a system is implemented, ADRs reports can be used systematically in regulatory decision-making including evaluating the impact of the HM classification policy by a study of the impact of the change on appearance of ADRs that the change was supposed to minimise.

Findings from Study Two, Study Three and Study Four showed that there are a number of factors that may impede implementation which need to be acknowledged by the officials in the Kuwaiti DRA prior to implementing the proposed recommendations. DRAs should employ people with the specialist knowledge and skills required to ensure effective medicine and HMs evaluation. Employees must be of integrity and should be well rewarded, mainly since medicine regulation involves various stakeholders with commercial interests who may try to apply pressure on the authority in order to secure decisions favourable to themselves (as reported in Study Four). Adequate and sustainable financing mechanisms are clearly crucial. All three studies has shown that shortage of qualified personnel is the main constrain in the DRA system. For effective implementation of the HM classification policy, this requires that the DRA have adequate numbers of qualified staff. The staff, specifically evaluators, should be knowledgeable enough to provide the required technical assistance [178].

In Study Three and Study Four, findings revealed that evaluators lacked training in dossier evaluation. Others also mentioned the lack in required herbal experience. The lack of staff in terms of quantity and quality has also been reported in reports investigating the Ugandan and the Mozambique DRAs [179]. Collaboration may be established, where appropriate, between the DRA and the country's educational institutions, to provide the number and types of medicine experts which are needed. The aim is not only to increase the number of reviewers, but also to develop skills through existing education and short training courses. Currently, the Pharmacy Department at Kuwait University (which is the only Pharmacy School in

the country) does not provide any courses in relation to pharmaceutical and herbal regulatory sciences [180]. A sensible step towards enhancing reviewers' knowledge and understanding of the regulatory system and its functions prior to working at the authority, is the possibility of the Kuwaiti MOH and DRA in collaboration with the school of pharmacy to review the pharmacy curriculum for undergraduate pharmacy course to include modules in regulatory education in medicines (including herbals) registration. A comprehensible, module-based educational package may be developed by collaboration between countries. The DRA may then choose where to send its employees for the training they most require.

Moreover, the information and knowledge needed for the regulation of HMs or a specific herbal product are usually available in countries where more advanced technologies can be acquired more easily [28]. This knowledge could be made available in the Kuwaiti DRA, which may help to reduce the regulatory workload. Human resources development programmes should be made available to help employees to improve their skills and knowledge, and they should also have access to the latest scientific information to facilitate their work [28]. With implementing the proposed HMs classification policy in Kuwait, this will require re-evaluation of HMs matching the proposed definition and redirecting all such products to be registered in one department (Herbal Department). This might suggest an increased number of applications to be evaluated in the Herbal Department, which may result in an increased backlog of pending registration dossiers and increased workload. Therefore, during the transition period, the use of external experts to review the pending dossiers maybe a possible solution for this problem to reduce the workload on the internal reviewers. Another option is for the KDFCA to increase the time period for existing products that requires a transfer.

Clearly, human resources alone are not sufficient to promote effective implementation. The results from Study Two and Study Four showed that insufficient appreciation of management towards staff is among the challenges encountered. This finding is supported by a study conducted by Ratanawijitrasin and Wondemagegnehu [28] in ten WHO member states which reported that the capacity of the regulatory authorities to perform their functions properly can be influenced by human resource remuneration. This finding is also supported by a study conducted by Hill and Johnson [181] indicating that regulatory efficiency depends on having staff who are motivated

by giving incentives. Therefore, a system of rewards can be implemented for reviewers based upon conducing an appropriate evaluation on the reviewer's performance.

Lack of managerial plans and interest in improving the system was also among the challenges encountered in Study Four. Researchers that investigated the public managerial sector in Kuwait found that the majority of organisations in Kuwait do not have specific procedures for evaluating the managerial development functions, and that was the main reasons why most managers in Kuwait lacked management skills, leading to deterioration in work performance and motivation in reforming the working systems [182, 183]. Researchers argued that organisations in Kuwait are "rigid, non-innovative… adhering to red-tape, valuing hierarchy of authority and having too many managers and supervisors and very few functional staff" [184]. In order to ensure successful implementation of the recommendations in the Kuwaiti DRA, management skill training in the Kuwaiti DRA should be a priority.

From Study Four it was revealed that the Kuwaiti DRA permits the applicant to establish the contact with the technical or/and managerial staff before the approval of the product. A study that examined the new pharmaceutical policy in Italy has shown that the contact between staff and applicants may allow the culture of corruption from creeping into the system [185]. It was also reported in the literature that in all government sectors in Kuwait, there is no separation between work and personal affairs and there is primacy of personal relationships over work relationship [184]. The Kuwaiti government should alleviate the problems of favouritism and personal loyalty by adopting a personnel policy that encourages performance, productivity and compliance. A practical effective tool to circumvent any distortion in the Kuwaiti DRA may be the use of an electronic system for handling the regulatory review procedures, which is deficient in the Kuwaiti DRA which would result in minimum contact between the reviewer and the agent [175]. In Study Three it was also reported that implementing an electronic review system in assessing HMs requirements and documentations in Bahrain has resulted in efficient evaluation and minimisation in errors and misplacing files. Therefore, implementing an electronic evaluation system in Kuwait might also result in reducing workload and increasing the efficiency of the process.

7.4.3 Implications for consumers

Medicine regulation is proposed to protect the public. Traditionally it has been known as a process involving two actors, the DRA and the industry. But policies that foster such arrangements may run the risk of generating corruption [28] (as shown in Study Four). In order to support effective medicine regulation, arrangements that foster the participation of independent third parties should be considered. As consumers are the end-users of medicines, all regulatory efforts should lead, ultimately, to protection of the consumer. Public interest groups or consumer groups can contribute to these efforts by participating in the development of regulatory policies. They can perform as independent attorney generals and protect the public from conflicts of interests from industry and regulators. Because of the highly technical nature of medicines and their information, support from the DRA and other organisations (e.g. MOH) is needed to empower consumers so that they can make an appropriate contribution.

For optimal use of HMs it is important that patients have access to information about their safe and effective use, particularly as the public can perceive HMs as safe despite documented evidence of precautions, interactions and side effects associated with some products [186]. Knowledge of these issues is important for consumers to allow them to make informed decisions about HMs. However, patients do not always seek information from healthcare professionals about herbal products and do not always disclose their use of them [187]. An ethnographic study of herbal products retailers in the US suggested there can be variable verbal information provided to consumers at the point of purchase, with the quality of information provided being unreliable and dependent on staff training and expertise [188]. Though the THR scheme would have a definite safety improvement in comparison with the current regulatory situation in Kuwait, under this scheme only the quality and safety of the product are demonstrated. Therefore, if the THR scheme is implemented in Kuwait, pharmacists need to ensure that consumers understand that certain herbal products are not tested for their clinical effectiveness in the same way as conventional medicines. The Kuwaiti DRA can provide published information on its official website educating consumers regarding the traditional- use registration. Similar to the THR scheme in the EU, the Kuwaiti DRA can also demand that manufacturers include a THR certification mark or the statements “traditional medicines” or “traditionally used” on the product’s label, indicating that the product effectiveness is based on evidence of

long history of traditional use and not on clinical efficacy. This is so that consumers are educated enough to make informed choices when purchasing HMs.

As explained in Chapter Two (Section 2.1.1), the cost of CAMs (including many HMs) in Kuwait is usually covered out of pocket, since private or social insurance programs do not cover such costs. From Study Four it was reported that the current HM registration under the Unclassified Department does not include pricing of products and therefore the manufacturer has the complete freedom to set any price. As there is no control on the market pricing of CAM, many products may be extremely overpriced because of the costs of advertising [189]. Implementing the proposed HM classification policy will result in all HMs to become registered under the Herbal Department where all products are required to be priced with specific margin value. The implementation of the new policy might therefore result in more affordable prices of HMs to consumers and patients in Kuwait.

7.5 Suggestions for Future Research

From this research it can be noted that there are areas in the literature that can be investigated further. Further research can be conducted to be more focused on identifying the consumption level of HMs in Kuwait (and other countries) and the level of awareness of their safety effects on the general public. Such an investigation can add value and evidence to the existing problem (lack of appropriate regulatory measures in the Kuwaiti DRA) and its implications on the public's safety.

Based on the findings of the literature review (Study Two), another suggested path for research is the inclusion of other stakeholders in the data collection process. Identified papers [35, 190- 195] showed that in addition to exploring regulators' perceptions, the views of healthcare professionals (such as pharmacists, nurses and doctors), agents from the herbal drug industry, researchers and sellers from health stores could be useful for informing policies concerning medicines. Ultimately, the regulation of medicines is there to protect the public. Therefore, a study could be performed among consumers and patient groups to assess their current perception of the process and their views on how the process might be improved for their benefit.

Study Three and Study Four adopted two exploratory case studies in two Gulf Cooperation Council (GCC) countries. In Study Three, it was revealed that the Bahraini classification of HMs was mostly based on the Saudi's DRA classification,

which aimed to facilitate a future GCC central registration system for HMs (i.e. similar to the EU central drug registration at the European Medicines Agency), which would allow authorisation of a single HM in all GCC member states at the same time, improving the regulatory approval processes and generating operational efficiencies at the national level [175]. An important opportunity for further research therefore may exist in the other four GCC countries; UAE, Saudi Arabia, Qatar, Oman and Yemen (as member in Health Council), in order to expand the findings of this study by conducting additional investigations of their HM registration systems to compare and generate comprehensive findings with the purpose of informing harmonisation of the HM registration across the GCC countries. The comparison could incorporate analysing the strengths, weaknesses, opportunities and threats of the HM registration system of each GCC authority which may yield necessary facts to consider when informing a harmonised HM registration system.

Evaluation of the change process itself is critical for the successful execution of the policy. As this thesis did not investigate the impact of the HM classification policy extensively, future research can include an evaluation of the impact of the THR scheme in Bahrain or other HMs importing countries (such as Egypt [196] and United Arab Emirates [197]). The technique carried out to evaluate the impact of the THR scheme in UK can be adopted, which consists of a survey of quality and safety information provided on the labels and patient information leaflets of HMs selected from pharmacies, supermarkets and health shops [198]. To evaluate the effect of the policy in Kuwait, this method can be carried out twice; prior to the implementation of the policy and after, where the findings from the two surveys can be compared. Such an evaluation could add value to its real-time validity and implications.

7.6 Reflections on the Research

Reflecting on the research is important to ensure that the research is credible and convincing. Having a personal reflection about the research enables researchers to consider ways their relationship with the participants have been affected by presumptions arising from those preconceptions [199]. This may include reflecting on assumptions the researcher may have made about the participants and their responses to the interview questions and how these assumptions influenced the interview process. It also includes how the values, belief, life experience and socio-economic

status of the researcher may have influenced the analytical process [199]. In this section, reflections on the research process are presented from the principal researcher's personal experience in conducting the research.

During the early stages of this research, an exploration of the HM registration laws had to be conducted to be able to identify how other countries define and classify HMs in their national DRAs (Study One). The first step that brought a high complexity to the research was to identify countries that would be suitable to compare. It had to be kept in mind that the chosen countries would not only have to be countries with well-established HM registration systems, it should also be countries with sufficient documentation to conduct the necessary desk research. For example, of the GCC members, Saudi Arabia has the most established DRA compared to Kuwait, Bahrain, Qatar, UAE, Oman and Yemen [200]. Moreover, the Saudi pharmaceutical market is considered one of the most growing markets internationally, and the most important market in the Middle-East [201]. Therefore it was thought useful to investigate how the Saudi DRA classify and define HMs. However, access of the official website of the Saudi DRA is limited to countries in the Middle-East, and therefore the researcher could not access the website from the UK. For the comparison, the researcher also had to be critical in determining which aspects were the comparable aspects of the policy to maintain the balance between the technical aspects and the policy level of the comparison. Moreover, in Study Three (Bahraini case study), although it had to be kept in mind that the chosen country would have to be with well-established DRA and a country that only imports HMs, however, most importantly, the researcher took into account that the country must be contactable and accessible for conducting the fieldwork/interviews. Bahrain being a neighbouring country to Kuwait, in which the researcher also understands their ways and culture, made it a favourable choice for investigation.

Due to the nature of the topic being discussed, in Study Three and Study Four, the researcher assumed that there might be some difficulty in getting the honest opinion of participants especially reviewers on issues raised towards the management during the semi-structured interviews. The researcher therefore, predicted that this might make the participants unwilling to disclose any sensitive information, thereby limiting the credibility of the research. This may have been worsened if the researcher had sought to obtain information from the participants in groups such as through focus

groups rather than individual interviews as the participants may have thought that other members of the group may report them. In order to overcome this difficulty, the researcher believed that data would be better obtained through semi-structured interviews rather than focus groups. The researcher also prepared to take notes rather than tape recording in case the participants declined being recorded. In addition, the researcher introduced herself to all the participants as a PhD student and a previous reviewer in the Kuwaiti DRA, but stated explicitly that the interviews were only for research purposes aimed at improving the HM registration system in Kuwait, as such should not implicate anyone. Even though these steps were taken, the researcher felt that some of the participants may still not have disclosed their honest opinions about the issues raised due to fear of being reported. In Bahrain for instance some of the participants refused to be tape-recorded. One stated that she was an ex-agent of one of the manufacturing companies and as such would not want her reputation to be implicated by the statements she may make. In this instance the researcher took notes. Also, some of the participants exhibited characteristics that showed that they did not want to take responsibility for giving information that may be incorrect by trying to confirm their views with that of the participants on issues discussed. For instance one participant asked the researcher if her perception was right; "*Doesn't it sound reasonable?"(K11).* In order to avoid introducing bias, the researcher maintained a neutral stand by not answering such questions; rather, the participants were reminded that they were no right or wrong answers.

In addition, the topic explored is a topic of great interest to the researcher who has prior knowledge of medicines registration and regulation in Kuwait and as such may make her more predisposed to follow discussions in this area with ease. However, this may have led the researcher to unintentionally expose her views about issues raised during the interviews or being judgemental about participants' responses. To overcome this issue, the researcher remained as open as possible and believed that it is possible for others to have a different perception of issues. In addition, since the researcher is a reviewer, the reviewers may have perceived the researcher as "one of them". This may have made the reviewers to feel more comfortable sharing information and thereby facilitating the data collection. Also, the researcher has many relatives and friends from Bahrain since her mother is Bahraini. This may have made many participants in Bahrain feel more comfortable speaking to the researcher as

shown from the comment from one of the participants; *"You are not only one of us, you are like my sister, I will help in any way" (K17).*

Another aspect that is reflected on by the researcher is the differentiation between 'good' and 'bad' HM classification policies that was done throughout the research in order to recommend the most appropriate policy for Kuwait. It was difficult to define exactly what is considered to be good and what is considered to be bad. The researcher took the understanding that countries from the EU (specially Germany) which are considered to have longstanding tradition in therapeutic use of herbs are advanced in HM science, research and education and have better regulation in the regulation of the HM legal framework which have been proven to be successful in their efforts in protecting the safety of the public than for example the US.

Looking back at the research that was conducted in Bahrain during the period of between October- November 2017, this limited time period had implications on the depth of the research. In the event that there had been more time to conduct the research, the researcher would have tried to investigate one or two more countries and conduct more observations/interviews for each of the countries. By adding more countries to the case study, the findings would have been more reliable, robust, and would have given further depth to the issue.

The concept of transferability was considered in this research. Transferability is a term used in qualitative research to refer to the "applicability of findings to other situations under similar, but not identical, conditions" [202]. Through the in-depth and detailed descriptions obtained from the participants who took part in the semi-structured interviews and observations, the researcher believes that the findings of the qualitative phase of this research may be of relevance in some broader contexts. This means that the findings arising from this research may not be applicable to only Kuwait but may be applicable to other similar areas. Therefore, the researcher made sure to explain to the reader throughout the thesis that that the findings and recommendations from this research can also be beneficial in other countries facing similar regulatory issues.

7.8 Concluding Remarks

The diversity of HMs regulations worldwide and the inadequate premarketing regulatory measures for evaluating HMs in some countries have an undesirable

ultimate effect on the public's health in countries that import HMs. Using existing and empirical evidence from DRAs with established HM registration systems, this thesis informed recommendations of a definition and suitable classification policy for imported HMs into Kuwait- a country with an unsophisticated HM registration system. This thesis also explored Kuwait's readiness for implementation and suggested a feasible implementation plan. Within the proposed policy, the manufacturer of a HM would have two main regulatory pathways for marketing in Kuwait; within medicine law a full application, or simplified registration as a traditional herbal medicinal product. Despite the impeding cultural and technical issues in the Kuwaiti DRA's current system, there is willingness from the officials to support the adoption and implementation of the suggested recommendations with the belief that the new policy would result in a regulatory clarification and consistency and an increased safety level. To promote regulatory harmonisation and to ensure that all HMs approved for sale are safe and of suitable quality globally, it is suggested that the policy recommendations from this thesis are implemented in other DRAs that lack such a policy. While this thesis sufficiently investigated the development and implementation stages of the policy, future work could focus on the final stage; evaluation of the policy.

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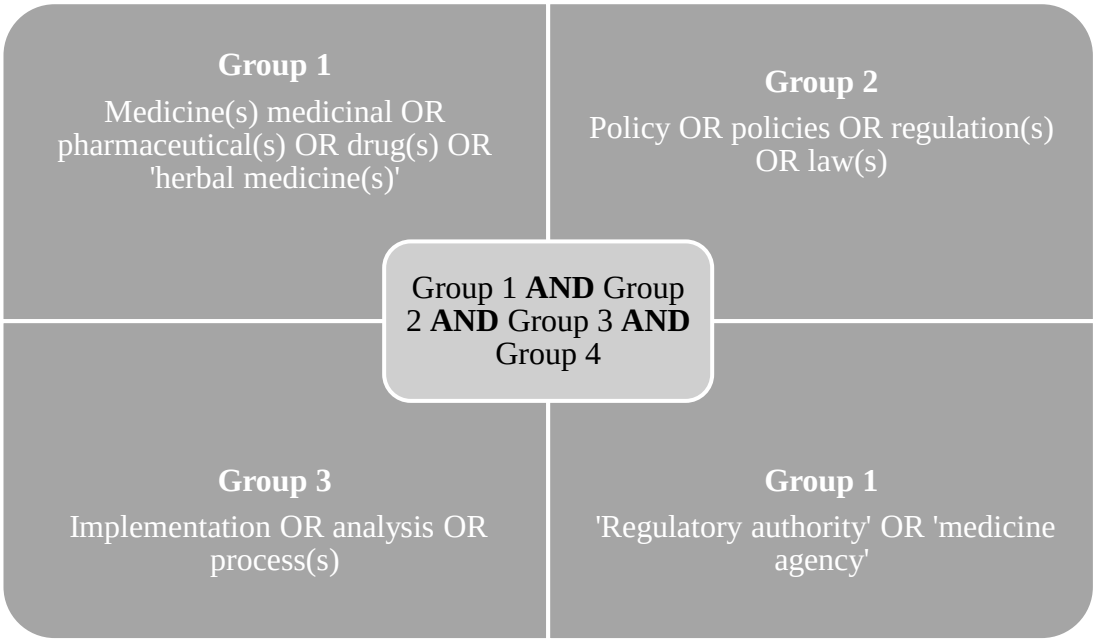
Thesis Appendices

Appendix 3.1: Literature review search strategy and keywords details



Appendix 3.2: Bahrain drug regulatory authority participant invitation letter

SUBJECT: INVITITATION TO PARTICIPATE IN THE RESEARCH PROJECT TITLED: DEVELOPING GUIDELINES FOR THE REGISTRATION OF HERBAL MEDICINES IN KUWAIT

Dear Sir/ Madam,

This is a letter of invitation to consider participating in a study I am conducting as part of my Doctoral degree in Pharmacy and Pharmaceutical Sciences at the University of Manchester, UK under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke. This study aims to explore current registration arrangements for herbal remedies (i.e. medicines which contain herbals as their active ingredient) and identify any possible shortcomings or challenges, in order to make recommendations for a suitable classification and conformity assessment procedure suitable for initial registration of imported, manufactured herbal medicines in Kuwait. To gain these insights, I am planning to conduct observations of the herbal products registration process, collect related documents and conduct some interviews with key officials at the National Health Regulatory Authority in Bahrain.

Before you decide to take part in this study, it is important for you to understand why the project is being conducted and what it will involve. Please take time to carefully read the attached Participant Information Sheet and discuss it with others if you wish.

If you decide to take part, then please complete and return the Informed Consent Declaration form attached and send it back through the following email:

AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK

If you have any enquiries about the study, then please do not hesitate to contact us through the following contact information:

AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +447449620025

I would like to assure you that this study has been reviewed and received ethics committee approval though the Research Ethics Review Board at the University of Manchester.

I very much look forward to speaking with you and thank you in advance for your assistance in this project.

Sincerely,
Azhar Alostad, MPharm, MSc
PhD student at Centre for Pharmacy Workforce Studies (CPWS)
Division of Pharmacy & Optometry
School of Health Sciences
Faculty of Biology, Medicine and Health
University of Manchester
Manchester M13 9PT, UK

Appendix 3.3: Kuwait drug regulatory authority participant invitation letter

SUBJECT: INVITITATION TO PARTICIPATE IN THE RESEARCH PROJECT TITLED: DEVELOPING GUIDELINES FOR THE REGISTRATION OF HERBAL MEDICINES IN KUWAIT

Dear Sir/ Madam,

This is a letter of invitation to consider participating in a study I am conducting as part of my Doctoral degree in Pharmacy and Pharmaceutical Sciences at the University of Manchester/ UK under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke. This study aims to explore the perceptions towards proposed recommendations of suitable classification and conformity assessment procedure for herbal medicines (HMs) registration and identify the factors that influence the readiness for these recommendations to be implemented in the Kuwait drug regulatory authority. To gain these insights, I am planning to conduct observations of the herbal products registration process, collect related documents and conduct some interviews with key officials at the Kuwait Drug and Food Control and administration in Kuwait.

Before you decide to take part in this study, it is important for you to understand why the project is being conducted and what it will involve. Please take time to carefully read the attached Participant Information Sheet and discuss it with others if you wish.

If you decide to take part, then please complete and return the Informed Consent Declaration form attached and send it back through the following email:

AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK

If you have any enquiries about the study, then please do not hesitate to contact us through the following contact information:

AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +447449620025

I would like to assure you that this study has been reviewed and received ethics committee approval though the Research Ethics Review Board at the University of Manchester.

I very much look forward to speaking with you and thank you in advance for your assistance in this project.

Sincerely,
Azhar Alostad, MPharm, MSc
PhD student at Centre for Pharmacy Workforce Studies (CPWS)
Division of Pharmacy & Optometry
School of Health Sciences
Faculty of Biology, Medicine and Health
University of Manchester
Manchester M13 9PT, UK

Appendix 3.4: Bahrain drug regulatory authority participant information sheet for interview

MANCHESTER 1824
The University of Manchester

Participant information sheet

Study title: Investigation of the current herbal medicine registration system in the Bahrain Drug Regulatory Authority

You are being invited to take part in a research study, which aims to evaluate the current registration system of herbal medicines (HMs) in Bahrain. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences, which is under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke at the University of Manchester, UK. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?
Azhar Alostad, PhD student at the University of Manchester, Manchester, UK.

What is the purpose of the research?
The purpose of the research is to evaluate the registration of HM in the Bahrain drug regulatory authority (DRA) and gain insights of challenges before the introduction of the new system, facilitators and barriers of the actual implementation of the classification guidelines and how this works now. This will then serve to inform recommendations for a suitable classification and conformity assessment procedure and implementation into the HMs registration department in the Kuwaiti DRA, which does not currently have such a system.

Why have I been chosen?
You have been chosen, as you are currently one of the key officials who are dealing directly with the registration of herbal products in the Pharmaceutical Product Regulation Department in the National Health Regulatory Authority (NHRA).

What would I be asked to do if I took part?
You will be asked to take part in an interview which will include a number of questions related to the design and implementation of herbal products classification guidelines. The interview will be audio-recorded, with your consent and transcribed verbatim. The consent form is attached.

What is the duration of the research?
You have up to 48 hours to decide whether to take part in the research. We expect that the interview will last for approximately 1 hour. Overall, data collection is being conducted between October 2017 and the end of January 2018.

Where will the research be conducted?
The interview will take place face-to-face at your place of work at the NHRA at somewhere private where others cannot overhear what is being said.

What happens to the data collected?
The researcher will anonymously transcribe the audio recording from the interview. In case of the interview being conducted in Arabic, a certified translator expert at Basira translation centre in Kuwait will perform the translation and transcription at once. After transcription, the recordings will be disposed of immediately The transcribed data will be crossed checked with the recordings by the researcher. After transcription, analysis of the anonymised data will start at the University of Manchester, UK. The audio recordings and transcripts will be stored on an encrypted server at the University of Manchester, UK. The researcher will then analyse the information gathered from the written transcriptions to look for common themes. We might use extracts of anonymous quotes in the final report or other publication to illustrate the identified themes. No information that can identify you will ever appear in any reports. At the end of the study and per request, we will be happy to offer you a short summary highlighting the main results of the study. Anonymised data will be stored for a minimum of 5 years and may be used to inform future research studies on similar topics.

How is confidentiality maintained?
We assure you confidentiality of the data collected. No one outside the research team will know what you have said or that you are participating in the study. The data will be analysed anonymously. Any personal information provided will

be anonymised. This means that your name will never be mentioned during the interview to guarantee anonymity and a code will be assigned for this purpose. Anonymised data collected will be stored on an encrypted secured network computer at the University of Manchester, UK. The audio-recordings data will be discarded once the data are transcribed, anonymised and analysed.

What happens if I do not want to take part or if I change my mind?
It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign the attached consent form. If you decide to take part, you are still free to withdraw up to the time of anonymization of transcripts and destruction of audio-recordings without giving a reason and without detriment to yourself.

Will the outcome of the research be published?
The outcome of the research will be written up as a PhD thesis. It is also proposed that some findings of this research will be published in academic/ professional/ regulatory journals.

Who has reviewed the research project?
The project has been reviewed by the researcher's two supervisors as well as two internal assessors from the University of Manchester, UK.

What if something goes wrong?
If at any point during the interview, you felt the need to stop, the interview will be paused to see if you wish to carry on or withdraw. A distress protocol will be followed thereafter. Please be assured that our policy is not to send the participants away from an interview feeling unhappy. If you have a concern about any aspect of this study, you should contact the researcher who will do their best to answer your questions.

What if I want to make a complaint?

Minor complaints
If you have a minor complaint then you need to contact myself (the researcher) in the first instance.
AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421

Alternatively, you can contact my supervisors:
DR ELLEN SCHAFHEUTLE, E-MAIL: ELLEN.SCHAFHEUTLE@MANCHESTER.AC.UK TEL: +441612757493
DR DOUGLAS STEINKE, E-MAIL: DOUGLAS.STEINKE@MANCHESTER.AC.UK TEL: +441612752324

Formal Complaints
If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the above individuals in the first instance then please contact the Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674 or 275 2046.

What Do I Do Now?
If you have any queries about the study or if you are interested in taking part then please contact

AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939]

Appendix 3.5: Kuwait drug regulatory authority participant information sheet for interview

MANCHESTER 1824
The University of Manchester

Participant information sheet

Study title: Investigation of the current herbal medicine registration system in the Kuwait Drug Regulatory Authority

You are being invited to take part in a research study, which aims to identify the factors affecting the readiness in the current herbal medicines (HM) registration department in Kuwait to implement proposed recommendations of suitable classification and conformity assessment procedure for HMs registration. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences, which is under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke, University of Manchester, UK. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?
Azhar Alostad, PhD student at the University of Manchester, Manchester, UK.

What is the purpose of the research?
The purpose of this research is to explore the perceptions of the officials towards the proposed recommendations of suitable classification and conformity assessment procedure for HMs registration and identify the factors that influence the readiness for these recommendations to be implemented in the Kuwait drug regulatory authority (DRA).

Why have I been chosen?
You have been chosen, as you are currently one of the key regulators who are dealing directly with the registration of herbal products in the Kuwait Food and Drug Control and Administration (KDFC) at somewhere private where others cannot overhear what is being said.

What would I be asked to do if I took part?
You will be asked to attend an interview, which will include a number of questions that will explore your perceptions on the recommendations for an improved HMs registration system in Kuwait in addition to the organisational and cultural issues that will be affected during policy implementation. The interview will be audio-recorded, with your consent and transcribed verbatim. The consent form is attached.

What is the duration of the research?
You have up to 48 hours to decide whether to take part in the research. We expect that the interview will last for approximately 1 hour. Overall, data collection is being conducted between May 2017 and the end of August 2018.

Where will the research be conducted?
The interview will take place face-to-face at your place of work at the KDFC.

What happens to the data collected?
The researcher will anonymously transcribe the audio recording from the interview. In case of the interview being conducted in Arabic, a certified translator expert at Basira translation centre in Kuwait will perform the translation and transcription at once. The transcribed data will be crossed checked with the recordings by the researcher. After transcription, analysis of the anonymised data will start at the University of Manchester, UK. The audio recordings and transcripts will be stored on an encrypted server at the University of Manchester, UK. The researcher will then analyse the information gathered from the written transcriptions to look for common themes. We might use extracts of anonymous quotes in the final report or other publication to illustrate the identified themes. No information that can identify you will ever appear in any reports. At the end of the study and per request, we will be happy to offer you a short summary highlighting the main results of the study. Anonymised data will be stored for a minimum of 5 years.

How is confidentiality maintained?
We assure you confidentiality of the data collected. No one outside the research team will know what you have said or that you are participating in the study. The data will be analysed anonymously. Any personal information provided will be anonymised. This means that your name will never be mentioned during the interview to guarantee anonymity and

a code will be assigned for this purpose. Anonymised data collected will be stored on an encrypted secured network computer at the University of Manchester, UK. The audio-recordings data will be discarded once the data are transcribed, anonymised and analysed.

What happens if I do not want to take part or if I change my mind?
It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign the attached consent form. If you decide to take part, you are still free to withdraw up to the time of anonymization of transcripts and destruction of audio-recordings without giving a reason and without detriment to yourself.

Will the outcome of the research be published?
The outcome of the research will be written up as a PhD thesis. It is also proposed that some findings of this research will be published in academic/ professional/ regulatory journals.

Who has reviewed the research project?
The project has been reviewed by the researcher's two supervisors as well as two internal assessors from the University of Manchester, UK.

What if something goes wrong?
If at any point during the interview, you felt the need to stop, the interview will be paused to see if you wish to carry on or withdraw. A distress protocol will be followed thereafter. Please be assured that our policy is not to send the participants away from an interview feeling unhappy. If you have a concern about any aspect of this study, you should contact the researcher who will do their best to answer your questions.

What if I want to make a complaint?

Minor complaints
If you have a minor complaint then you need to contact myself (the researcher) in the first instance.
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What Do I Do Now?
If you have any queries about the study or if you are interested in taking part then please contact
AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939]

Appendix 3.6: Bahrain drug regulatory authority participant information sheet for observation

MANCHESTER 1824
The University of Manchester

Participant information sheet

Study title: Investigation of the current herbal medicine registration system in the Bahrain Drug Regulatory Authority

You are being invited to take part in a research study, which aims to evaluate the current registration system of herbal medicines (HMs) in Bahrain. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences, which is under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke at the University of Manchester, UK. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?
Azhar Alostad, PhD student at the University of Manchester, Manchester, UK.

What is the purpose of the research?
The purpose of the research is to evaluate the registration of HM in the Bahrain drug regulatory authority (DRA) and gain insights of challenges before the introduction of the new system, facilitators and barriers of the actual implementation of the classification guidelines and how this works now. This will then serve to inform recommendations for a suitable classification and conformity assessment procedure and implementation into the HMs registration department in the Kuwaiti DRA, which does not currently have such a system.

Why have I been chosen?
You have been chosen, as you are currently one of the key officials who are dealing directly with the registration of herbal products in the Pharmaceutical Product Regulation Department in the National Health Regulatory Authority (NHRA).

What would I be asked to do if I took part?
The researcher will observe you carrying out your daily routinely activities related to the registration process of HMs. The purpose is to observe you registering and assessing herbal products. During the observation process, the researcher might ask you some questions related to the task you are carrying at that time. This will help in understanding and evaluating the current registration process. The researcher will take notes as the observation proceeds, but no confidential details or identity will be recorded. As observations will be taking place over a number of sessions, ongoing consent is asked for at the start of each session. If you decided to participate, your consent will be taken verbally.

What is the duration of the research?
We expect that the overall observation period at the NHRA last up to 2 months. The observation duration in each department will depend on the task you carry at the time of the observation and will end until saturation of data is reached.

Where will the research be conducted?
The observation will take place face-to-face at your place of work at the NHRA.

What happens to the data collected?
Notes taken during the observations will be stored on an encrypted server at the University of Manchester, UK. The researcher will then analyse the information gathered from the written notes to look for common themes and illustrate a clear description of the registration process of HMs. No information that can identify you will ever appear in any reports. At the end of the study and per request, we will be happy to offer you a short summary highlighting the main results of the study. Anonymised data will be stored for a minimum of 5 years and may be used to inform future research studies on similar topics.

How is confidentiality maintained?
We assure you confidentiality of the data collected. No one outside the research team will know what you have said or that you are participating in the study. The data will be analysed anonymously. Any personal information provided will be anonymised. This means that your name will never be mentioned on the notes taken during the observation process

to guarantee anonymity and a code will be assigned for this purpose. Anonymised data collected will be stored on an encrypted secured network computer at the University of Manchester, UK. The notes will be discarded once the data are transcribed, anonymised and analysed.

What happens if I do not want to take part or if I change my mind?
It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign the attached consent form. If you decide to take part, you are still free to withdraw up to the time of the data analysis stage without giving a reason and without detriment to yourself.

Will the outcome of the research be published?
The outcome of the research will be written up as a PhD thesis. It is also proposed that some findings of this research will be published in academic/ professional/ regulatory journals.

Who has reviewed the research project?
The project has been reviewed by the researcher's two supervisors as well as two internal assessors from the University of Manchester, UK.

What if something goes wrong?
If at any point during the observation, you felt the need to stop, the observation will be paused to see if you wish to carry on or withdraw. Please be assured that our policy is not to leave the participants feeling unhappy. If you have a concern about any aspect of this study, you should contact the researcher who will do their best to answer your questions. Please note that during observations, if the researcher witnesses any activity that breaches the regulation or is likely to prove any danger, then the researcher will examine the activity and where there might be a duty to report, the researcher shall report to the relevant body.

What if I want to make a complaint?

Minor complaints
If you have a minor complaint then you need to contact myself (the researcher) in the first instance.
AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421
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Formal Complaints
If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the above individuals in the first instance then please contact the Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674 or 275 2046.

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This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939]

Appendix 3.7: Kuwait drug regulatory authority participant information sheet for observation

MANCHESTER 1824
The University of Manchester

Participant information sheet

Study title: Investigation of the current herbal medicine registration system in the Kuwait Drug Regulatory Authority

You are being invited to take part in a research study, which aims to identify the factors affecting the readiness in the current herbal medicines (HM) registration department in Kuwait to implement proposed recommendations of suitable classification and conformity assessment procedure for HMs registration. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences, which is under the supervision of Dr Ellen Schafheutle and Dr Douglas Steinke, University of Manchester, UK. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for taking the time to read this.

Who will conduct the research?
Azhar Alostad, PhD student at the University of Manchester, Manchester, UK.

What is the purpose of the research?
The purpose of this research is to explore the perceptions of the officials towards the proposed recommendations of suitable classification and conformity assessment procedure for HMs registration and identify the factors that influence the readiness for these recommendations to be implemented in the Kuwait drug regulatory authority (DRA).

Why have I been chosen?
You have been chosen, as you are currently one of the key regulators who are dealing directly with the registration of herbal products in the Kuwait Food and Drug Control and Administration (KDFC).

What would I be asked to do if I took part?
The researcher will observe you carrying out your daily routinely activities related to the registration process of HMs. The purpose is to observe you registering and assessing herbal products. During the observation process, the researcher might ask you some questions related to the task you are carrying at that time. This will help in understanding the current registration process and identify any gaps found. The researcher will take notes as the observation proceeds, but no confidential details or identity will be recorded. As observations will be taking place over a number of sessions, ongoing consent is asked for at start of each session. If you decided to participate, you consent will be taken verbally.

What is the duration of the research?
We expect that the overall observation period at the KDFC last up to 2 months. The observation duration in each department will depend on the task you carry at the time of the observation and will end until saturation of data is reached.

Where will the research be conducted?
The observation will take place face-to-face at your place of work at the KDFC.

What happens to the data collected?
Notes taken during the observations will be stored on an encrypted server at the University of Manchester, UK. The researcher will then analyse the information gathered from the written notes to look for common themes and illustrate a clear description of the registration process of HMs. No information that can identify you will ever appear in any reports. At the end of the study and per request, we will be happy to offer you a short summary highlighting the main results of the study. Anonymised data will be stored for a minimum of 5 years and may be used to inform future research studies on similar topics.

How is confidentiality maintained?
We assure you confidentiality of the data collected. No one outside the research team will know what you have said or that you are participating in the study. The data will be analysed anonymously. Any personal information provided will be anonymised. This means that your name will never be mentioned on the notes taken during the observation process

to guarantee anonymity and a code will be assigned for this purpose. Anonymised data collected will be stored on an encrypted secured network computer at the University of Manchester, UK. The notes will be discarded once the data are transcribed, anonymised and analysed.

What happens if I do not want to take part or if I change my mind?
It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign the attached consent form. If you decide to take part, you are still free to withdraw up to the time of the data analysis stage without giving a reason and without detriment to yourself.

Will the outcome of the research be published?
The outcome of the research will be written up as a PhD thesis. It is also proposed that some findings of this research will be published in academic/ professional/ regulatory journals.

Who has reviewed the research project?
The project has been reviewed by the researcher's two supervisors as well as two internal assessors from the University of Manchester, UK.

What if something goes wrong?
If at any point during the observation, you felt the need to stop, the observation will be paused to see if you wish to carry on or withdraw. Please be assured that our policy is not to leave the participants feeling unhappy. If you have a concern about any aspect of this study, you should contact the researcher who will do their best to answer your questions. Please note that during observations, if the researcher witnesses any activity that breaches the regulation or is likely to prove any danger, then the researcher will examine the activity and where there might be a duty to report, the researcher shall report to the relevant body.

What if I want to make a complaint?

Minor complaints
If you have a minor complaint then you need to contact myself (the researcher) in the first instance.
AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421
Alternatively, you can contact my supervisors:
DR ELLEN SCHAFHEUTLE, E-MAIL: ELLEN.SCHAFHEUTLE@MANCHESTER.AC.UK TEL: +441612757493
DR DOUGLAS STEINKE, E-MAIL: DOUGLAS.STEINKE@MANCHESTER.AC.UK TEL: +441612752324

Formal Complaints
If you wish to make a formal complaint or if you are not satisfied with the response you have gained from the above individuals in the first instance then please contact the Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing: research.complaints@manchester.ac.uk or by telephoning 0161 275 2674 or 275 2046.

What Do I Do Now?
If you have any queries about the study or if you are interested in taking part then please contact
AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK TEL: +441612752421

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939].

Appendix 3.8: Bahrain and Kuwait drug regulatory authorities' observation guide

Observation Guide

Date	
Time	
Name of the drug regulatory authority	
Name of Department	
Participant Code	
Name of activity	
Number of activity	

Description of task	
Requirements/documents required for the task	
Estimated timeline for completing the task	

Appendix 3.9: Bahrain drug regulatory authority interview consent form

MANCHESTER 1824
The University of Manchester

Participant consent form

Study title: Investigation of the current herbal medicine registration system in the Bahrain Drug Regulatory Authority

If you are happy to participate, please complete and sign the consent form below.

	Please initial box
1. I confirm that I have read the attached information sheet on the above project and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2. I understand that my participation in the study is voluntary and that I am free to withdraw anytime up to the time of anonymization of transcripts and destruction of audio-recordings without giving a reason and without detriment to myself.	
3. I understand that the outcome of the research will be written up as a PhD thesis and that some findings of this research will be published in academic/ professional/ regulatory journals.	
4. I understand that the anonymised data generated from this study may be used to inform future research studies on similar topics.	
5. I understand that my personal data will remain confidential.	
6. I understand that the interview will be audio-recorded.	
7. I agree to the use of anonymous quotes.	
8. I agree to take part in the above project	

Name of participant	Date	Signature
Name of researcher	Date	Signature

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939]

Appendix 3.10: Kuwait drug regulatory authority interview consent form

MANCHESTER 1824
The University of Manchester

Participant consent form

Study title: Investigation of the current herbal medicine registration system in the Kuwait Drug Regulatory Authority

If you are happy to participate, please complete and sign the consent form below.

	Please initial box
1. I confirm that I have read the attached information sheet on the above project and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.	
2. I understand that my participation in the study is voluntary and that I am free to withdraw anytime up to the time of anonymization of transcripts and destruction of audio-recordings without giving a reason and without detriment to myself.	
3. I understand that the outcome of the research will be written up as a PhD thesis and that some findings of this research will be published in academic/ professional/ regulatory journals.	
4. I understand that my personal data will remain confidential.	
5. I understand that the interview will be audio-recorded.	
6. I agree to the use of anonymous quotes.	
7. I agree to take part in the above project	

Name of participant	Date	Signature
Name of researcher	Date	Signature

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939]

Appendix 3.11: Bahrain drug regulatory authority interview guide

FOR DECISION MAKERS

Individual Background and Role

How long have you worked at the Agency? What is your current role?

The design, production and decision making of the classification of herbal products in NHRA:

1) How was the definition, the assessment procedure and classification of herbal products registration designed? Was it influenced by another system for example in another country?
    a. When was it introduced?
    b. Who designed it? Who were the decision makers from your team that were involved in the production of the policy?
    c. Were there any high-level initiatives or goals that prompted the decision to produce the policy? For example, was this decision motivated by a company-wide vision? How was it approved?
    d. What was the criteria you used when making the decision to produce the classification policy? For example; Were you comparing alternative solutions? Which ones?
2) Would you describe a few of the reasons you decided to produce this policy?

Facilitators and barriers of the production of the policy:

3) Were there any challenges that occurred while producing the policy? Did you notice anything exceptional or any points of friction?
4) What factors (or persons) facilitated the production of the policy?

The implementation process of the classification:

5) Can you explain to me the implementation process of the policy?
    a. When was the policy implemented?
    b. How was the policy implemented? What were the actual activities that were carried out?
    c. Who were the people involved in the implementation process?
    d. How is the implementation monitored and evaluated?
    e. Did the registration structure change? If so, how did the structure change? What was added?
6) What were the resources that were important to be available in order for the policy to be successfully implemented? (for example; availability of standing operating procedures or internal experts and consultants)
7) Were there any challenges that occurred while implementing the policy? Did you notice anything exceptional or any points of friction?
4) What factors (or persons) facilitated the implementation of policy?
8) From your experience, what strategies should be implemented to ensure that the classification policy achieves its intended purposes?

Views and perceptions:

9) What is your opinion about the current classification of herbal products? Do you think that it needs to be improved? If so, what needs improvement and why?
10) Please tell me about any other related challenges and problems with the current registration system of herbal products at the NHRA that you think needs to be addressed?
11) Please tell me about any strengths of the current HM registration system?
12) Please tell me about any weaknesses of the current HM registration system?
13) Please tell me about any threats that you think that might impede the performance of the current HM registration system?
14) Please tell me about any opportunities you that the current HM registration system have?
15) Do you have any knowledge about the assessment procedure for the registration of HMs in Kuwait? (the researcher will provide a brief explanation about the herbal product registration process in Kuwait)

16) Do you think that the classification and definition of HMs used in Bahrain could be implemented in Kuwait? Why?

End comments

17) Do you have any feature requests or suggestions for the registration process in Kuwait?
18) Is there anything else you might want me to know in relation to this, which maybe I haven't asked about?

FOR SCIENTIFIC REVIEWERS

Individual Background and Role:

How long have you worked at the Agency? What is your current role?

HMs current registration process in the NHRA:

1) Can you please explain briefly the herbal products registration procedure in the NHRA?
2) Could you please state how herbal products are defined and classified in the NHRA and according to what? And the main herbal products registration requirements?
3) How many herbal products were registered since the implementation of the pharmaceutical products classification policy?

The implementation process of the classification policy:

4) How was the policy implemented? What were the actual activities that were carried out?
5) Did the registration structure change after the implementation of the policy? If so, how did the structure change?
6) Who were the people involved in the implementation process?
7) Were you trained for the implementation of the policy? If so, what kind of training did you receive?
8) Is the implementation monitored and evaluated? If so, how is the implementation monitored and evaluated?

Facilitators and barriers of the implementation:

9) In your experience, have you experienced any problems or challenges while using the guideline in practice? If so, did you or other officials of the working group find ways to overcome these challenges? How?
10) What were the factors (or persons) that made the implementation of this policy easier?
11) What were the resources that were important to be available in order for the policy to be successfully implemented? (for example; availability of standing operating procedures or internal experts and consultants)

Views and perceptions:

12) What is your opinion about the current classification of herbal products? Do you think that it needs to be improved? If so, what needs improvement and why?
13) Please tell me about any other related challenges and problems with the current registration system of herbal products at the NHRA that you think needs to be addressed?
14) Do you have any knowledge about the assessment procedure for the registration of HMs in Kuwait? (the interviewer will provide a brief explanation about the herbal product registration in Kuwait)
15) Do you think that the classification and definition of HMs used in Bahrain could be implemented in Kuwait? Why?

End comments

16) Do you have any feature requests or suggestions for the registration process in Kuwait?
17) Is there anything else you might want me to know in relation to this, which maybe I haven't asked about?

Appendix 3.12: Kuwait drug regulatory authority interview guide

Individual Background and Role:
How long have you worked at the authority? What is your current role?

(1- 3 for scientific reviewers only)

HMs registration process in the KDFC

1) Can you please explain briefly the herbal products registration procedure in the KDFC?
2) Could you please state how herbal products are defined and classified in the KDFC and according to what? And the main herbal products registration requirements?
3) How many herbal products were registered in the past five years?

Views and perceptions on the recommendations

4) What is your opinion about the current procedure of classifying and registering HMs? Do you think that it needs to be improved? If so, what needs improvement and why?

   About the proposed recommendations of classification policy and conformity assessment procedures which had been given to the participant prior to the interview.

5) Do you think that these recommendations could be implemented in Kuwait? Why?
6) In your opinion, what are the benefits of these recommendations if they are to be implemented in the KDFC?

Policies and Procedures

7) In your opinion, how does the senior management encourage policy development in order to implement an effective policy?
8) In your opinion, is the management open or pay attention to the suggestions of the before implementing a policy?
9) In your opinion, how will the ministry of health (MOH) intervene on implementing the recommendations in the KDFC?
10) Within the KDFC, would you say there is an engaged and consistent decision making approach by the MOH?

(11- 18 for decision makers only)

11) At what levels (s) do you observe the KDFC's activities relating to programme decision making?
12) Does the MOH employ a standard structured approach to policy decision making? Are items such as: SOP's, guidance documents, templates or other decision making tools used? Do you think the MOH approach is mirrored by other similar organisations?
13) Within your circle of influence, how would you best describe the policy decision making approach within the KDFC? Are there traditional or cultural or hierarchical considerations that need to be adhered to?
14) Within the MOH, do groups, such as committees, task-forces or review panels play a key role in the policy decision making process for the KDFC? Please elaborate.
15) If you had to quantify in rough percentages the different contributing factors influencing a decision for a policy, what would be your estimate?
    Political % Financial % Scientific % Strategic % Other
16) Have you used techniques such as statistical modeling, SWOT analyses, scenario planning, brainstorming, sensitivity analyses or other structured approach in your decision making?
17) Have you received any formal training on Decision Making techniques? If yes, please elaborate.
18) If these recommendations were proposed to the MOH for adopting, how will the decision of adopting the policy be handled?

Organisational resources

19) In your opinion, what kind of resources that have to be in place in order for these recommendation to be successfully implemented?

Organisational structure

20) In your opinion, what will be changed in the foundation of the KDFC infrastructure if these recommendations are to be implemented?

Organisational culture

21) In your opinion, what are the cultural challenges that could face the authority when implementing the recommendations?
22) How do you think these cultural challenges can be overcome?
23) In your opinion, how does the organisational culture influence the implementation of a policy?

Organisational policies

24) In your opinion, what are the regulatory and procedural tensions that could face the KDFC when approving the recommendations? And in your opinion what would be the best way for approving the proposed recommendations?

Past experience

25) From your experience, what were the main issues that affected policy implementation into practice in general that need to be considered?

Appendix 3.13: University of Manchester Research Ethics Committee (UREC) approval to conduct research

Research Governance, Ethics and Integrity
2nd Floor Christie Building
The University of Manchester
Oxford Road
Manchester
M13 9PL
Tel: 0161 275 2206/2674
Email: research.ethics@manchester.ac.uk

Ref: 2017-1086-3939

03/10/2017

Dear Miss Azhar Alostad, , Dr Ellen Schafheutle, Dr Douglas Steinke

Study Title: DEVELOPING GUIDELINES FOR THE REGISTRATION OF HERBAL MEDICINES

University Research Ethics Committee 2

I write to thank you for submitting the final version of your documents for your project to the Committee on 28/09/2017 12:06 . I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form and supporting documentation as submitted and approved by the Committee.

Please see below for a table of the title, version numbers and dates of all the final approved documents for your project:

Document Type	File Name	Date	Version
Additional docs	Distress policy	03/07/2017	1
Additional docs	KDFC permission to conduct research	14/07/2017	1
Additional docs	List of references	14/07/2017	1
Additional docs	Translation office certification	25/07/2017	1
Lone Worker Policy/Procedure	Lone working and risk assessment	26/07/2017	1
Consent Form	Interview consent form for Bahrain	26/07/2017	1
Consent Form	Interview consent form for Kuwait	26/07/2017	1
Additional docs	NHRA permission to conduct research	01/08/2017	1
Consent Form	Consent form for officials found in the observation of the registration process in Bahrain	01/08/2017	1
Consent Form	Consent form for officials found in the observation of the registration process in Kuwait	01/08/2017	1
Additional docs	Data collection tool for drug registration evaluation to use in Bahrain during data collection	02/08/2017	1
Topic Guide	Interview topic guide for Bahrain and Kuwait	13/09/2017	2
Advertisement	Participant email invitation for bahrain	27/09/2017	3
Advertisement	Participant email invitation for kuwait (1)	27/09/2017	3
Advertisement	In process observation poster for Bahrain	27/09/2017	2
Advertisement	In process observation poster for Kuwait	27/09/2017	2
Participant Information Sheet	PIS for Bahrain interview (3)	27/09/2017	3
Participant Information Sheet	PIS for Kuwait interview	27/09/2017	3
Participant Information Sheet	PIS for Bahrain observation	27/09/2017	3
Participant Information Sheet	PIS for Kuwait observation	27/09/2017	3

This approval is effective for a period of five years however please note that it is only valid for the specifications of the research project as outlined in the approved documentation set. If the project continues beyond the 5 year period or if you wish to propose any changes to the methodology or any other specifics within the project, an application to seek an amendment must be submitted for review. Failure to do so could invalidate the insurance and constitute research misconduct.

You are reminded that, in accordance with University policy, any data carrying personal identifiers must be encrypted when not held on a secure university computer or kept securely as a hard copy in a location which is accessible only to those involved with the research.

Reporting Requirements:

You are required to report to us the following:

1. Amendments
2. Breaches and adverse events
3. Notification of progress/end of the study

Feedback

It is our aim to provide a timely and efficient service that ensures transparent, professional and proportionate ethical review of research with consistent outcomes, which is supported by clear, accessible guidance and training for applicants and committees. In order to assist us with our aim, we would be grateful if you would give your view of the service that you have received from us by completing a **UREC Feedback Form**. Instructions for completing this can be found in your approval email.

We wish you every success with the research.

Yours sincerely,

Dr Karen Lythe

Secretary to University Research Ethics Committee 2

Appendix 3.14: UREC amended approval

From: donotreply@infonetica.net
Sent: 15 June 2018 11:45
To: Azhar Alostad; Douglas Steinke; Ellen Schafheutle
Cc: University Research Ethics Committee 2
Subject: APPROVED: UREC Amendment Ref: 2018-1086-6401 (Automatic Email from the UoM Ethical Review Manager (ERM) system)

****Please ensure you read the contents of this message. This email has been sent via the Ethical Review Manager (ERM) system on behalf of the University of Manchester.****

Dear Miss Azhar Alostad,

Thank you for submitting your amendment request on 11/06/2018 14:43 for project: 2018-1086-6401 ; entitled: DEVELOPING GUIDELINES FOR THE REGISTRATION OF HERBAL MEDICINES which has now been approved. Your documentation has been suitably updated to reflect the proposed changes, please ensure you use this documentation.

Please note that if you have submitted revised supporting documents to accompany your amendment request, the approved versions of these are listed in a table below.

We wish you every success with the research.

Best wishes,

Mrs Genevieve Pridham

Secretary to University Research Ethics Committee 2

Appendix 3.15: Permission to conduct research at the Bahraini drug regulatory authority

RE: Permission letter to conduct research
Roaya Al Abbasi [roaya.alabbasi@nhra.bh]
Sent: Sunday, July 30, 2017 12:13 PM
To: Azhar Alostad; Azhar Naseeb [azhar.naseeb@nhra.bh]
Cc: Ellen Schafheutle; Douglas Steinke; CEO Secretary [CEOSecretary@nhra.bh]

Dear Azhar,

Thank you for your e-mail.

Please be noted that NHRA has no objection in allowing to conduct your research here. However please follow Bahrain rules & regulations in order to avoid any unfortunate events. NHRA will provide the support & co-operation of their staff members to facilitate your research.

Best Regards,

Roaya Al Abbasi
Chief,Pharmaceutical Product Regulation
Direct: +973 17 11 32 92 eMail: roaya.alabbasi@nhra.bh
Tel: +973 17 11 33 33 Fax: +973 17 11 32 73
Website: www.nhra.bh
P.O.Box: 11464, Manama, Kingdom of Bahrain

From: Azhar Alostad [mailto:azhar.alostad@postgrad.manchester.ac.uk]
Sent: 27 July 2017 01:17
To: Roaya Al Abbasi; CEO Secretary; Nabeela Ahmed; Mohamed Emam; Azhar Naseeb
Cc: Ellen Schafheutle; Douglas Steinke
Subject: Fwd: Permission letter to conduct research

Please find attached requested documents in this forwarded email.

Once again, your support is highly appreciated.

Kindest regards,

Azhar Alostad
Begin forwarded message:

> **From:** "Azhar Alostad" <azhar.alostad@postgrad.manchester.ac.uk>
> **To:** "CEO Secretary" <CEOSecretary@nhra.bh>
> **Cc:** "Azhar Naseeb" <azhar.naseeb@nhra.bh>, "Ahmed AlMulla" <ahmed.almulla@nhra.bh>
> **Subject: RE: Permission letter to conduct research**
>
> Dear Maisa,
>
> Many thanks for your email and for the NHRA response regarding permission to conduct research.
>
> **First**, Regarding the requested documents:
>
> 1- My supervisor will contact your Authority by Email to provide you with a formal request for permission to conduct research at the NHRA.
> 2- Please see attached registration letter from the University confirming that I am currently a fully registered PhD student at the University of Manchester and my Scholarship letter from the Kuwait cultural office.
> 3, 4 & 5- I am currently applying for the University of Manchester Research Ethics Committee (UREC) approval to conduct the research at the NHRA. The UREC application consists of a systematic detailed application of the research that will be conducting in the NHRA including data collection process, confidentiality, participant information sheets, and consent forms and management of data collected which I have also attached to this email.(Please see attached protocol and data collection procedures). For your reference, I have attached a format of the expected UREC approval letter. Once I receive the formal approval, a copy of the UREC approval letter will be sent to the NHRA. To fulfil the requirements of the PhD, some aspects of the research will be published in scientific peer-reviewed journals, however, any personal information provided will be anonymised and confidential, in interviews, a code will be assigned to each interview for this purpose. The recorded data will

be uploaded to a secured computer in the University of Manchester. After transcription, coding and anonymising the data, the records will be disposed of immediately.
6- Please see attached CV.

Second, can I please ask your authority to re-send the response in English indicating the remaining requested documents, the UREC will need to read the enquiries requested from your authority in order to provide me with ethical approval. Once you send the response in English, I will attach it to the UREC application.

Once again, I highly appreciate your help and valuable time in this matter. I look forward to receiving your response in English.

If you require any further information, please do not hesitate to contact me.

Kindest regards,
Azhar Alostad, MPharm, MSc
PhD student at Centre for Pharmacy Workforce Studies (CPWS)
Division of Pharmacy & Optometry
School of Health Sciences
Faculty of Biology, Medicine and Health
University of Manchester
Manchester M13 9PT, UK
Telephone: 0161 275 2421

From: CEO Secretary [CEOSecretary@nhra.bh]
Sent: Wednesday, July 12, 2017 8:39 AM
To: Azhar Alostad
Cc: Azhar Naseeb; Ahmed AlMulla
Subject: RE: Permission letter to conduct research

الأخت الفاضلة الصيدلانية أزهـار الأستاذ المحترمة

السلام عليكم و رحمة الله وبركاته،،،

تجدون أدناه رد الهيئة الوطنية لتنظيم المهن والخدمات الصحية بخصوص طلبكم:

الموضوع: موافقة مبدئية لعمل بحث الدكتوراه "دراسة نظام التسجيل الأدوية العشبية المحسنة في الهيئة الوطنية لتنظيم المهن والخدمات الصحية بمملكة البحرين"

إشارة إلى الموضوع أعلاه يطيب لي إفادتكم علماً بأنه لا يوجد لدينا مانع من عمل بحث الدكتوراه "دراسة نظام التسجيل للأدوية العشبية المحسنة في الهيئة الوطنية لتنظيم المهن والخدمات الصحية بمملكة البحرين".

وعليه نرجو منكم تزويدنا بالآتي من أجل الحصول على الموافقة النهائية:

1. التقدم لنا بطلب رسمي عن طريق الجامعة خاصتكم.
2. خطاب من الجامعة يفيد بأنكم قيد برنامج الدكتوراه لديهم.
3. تعهد رسمي من الجامعة ومنكم باستخدام جميع المعلومات والبيانات لصالح بحث الدكتوراه فقط وليست للنشر أو أي أمر آخر.
4. بروتوكول الدراسة المزمع عملها في مملكة البحرين مفصلاً ومعتمد من الجامعة.
5. نسخة من أدوات جمع بيانات البحث.
6. السيرة الذاتية خاصتكم.

كما نرجو منكم التنسيق والتواصل مع رئيس قسم تنظيم المواد الصيدلانية لدينا الصيدلانية رؤيا العباسي التي سوف تكون خير عون لكم في هذا الشأن
على هاتف رقم 17113292و بريد إلكتروني: roaya.alabbasi@nhra.bh

لذا، ولحين موافاتنا بجميع المتطلبات المذكورة أعلاه لن تتمكن الهيئة من إصدار الموافقة النهائية، وإنما هذه موافقة مبدئية أعطيت لكم بناء على طلبكم.

شاكرين ومقدرين تعاونكم و تفهمكم،،،
وتفضلوا بقبول فائق التحية والتقدير،،،

DISCLAIMER: "This communication is intended only for the named recipient and others authorized to receive it. It contains confidential or legally privileged information. If you are not the intended recipient, please notify us immediately, and note that any disclosure, copying, distribution or action you may take in reliance on this communication is strictly prohibited and may be unlawful. Unless indicated otherwise, this communication is not intended, nor should it be taken to create any legal and/or contractual relation or otherwise. National Health Regulatory Authority (NHRA) is neither liable for the proper and complete transmission of the communication, nor for any delay in its receipt. Whilst NHRA undertakes all reasonable efforts to screen outgoing e-mails for viruses, it cannot be held liable for any viruses transmitted by this e-mail."

Appendix 3.16: Permission to conduct research at the Kuwaiti drug regulatory authority

Ministry Of Health
Drug & Food Control
Pharmaceutical & Herbal Medicines
Registration & Control Admn

وزارة الصحـــــــــة
الرقابة الدوائية والغذائية
إدارة تسجيل ومراقبة الأدوية
الطبية والنباتية

Reference: CDC 005 ..... الرقم : .....

Date : 5/7/2017 ...../...../..... التاريخ :

To: The University of Manchester Review Ethics Committee

Dear Sir,

The Kuwait Drug and Food Control and Administration (KDFC) have no objection on the fieldwork and data collection of Miss Azhar Alostad who is a PhD student at the University of Manchester/ UK. Shay may conduct observational studies, collect related documents and conduct interviews with employees at the KDFC concerning her research on herbal medicine's registration. We will gladly provide her with all information and facilities that she requires to fulfil her research requirements and standards.

Thank you for your cooperation.

Kind regards,

Ph. Ramy S. Behbehani
Medicines Laboratory Superintendent
Drug & Food Control Administration

Ph. Ramy S. Behbehani

Medicines Laboratories Superintendent

MSc, BSc(Honr) Pharmacy

E Mail: r.behbehani@moh.gov.kw

Appendix 3.17: Observation distress policy

Observation distress policy
Participant number _____ Date _____ Experimenter _____

Administer 1st mood rating

Has the observation been stopped because the participant became distressed? Yes/no

If yes: Report to supervisor, who will *report to the committee at the conclusion of the study*.

Ask: Comments or questions about the study? How is the participant feeling? Is their mood at normal levels?

Explain: Our policy is not to leave the participant in an observation feeling unhappy.

Review:

- If participant feels able to carry on; resume observation
- If participant is unable to carry on; go to Administer 2nd mood rating

Administer 2nd mood rating. Had the participant indicated they are unhappy (levels 8-9), anxious (levels 1-2), or despondent (levels 1-2)? Yes/no

If yes: is this lower than their 1st mood rating? Yes/no

If yes:

(1) Ask participant to accompany to a quiet area and ask the participants how they are feeling, listen with empathy.

(2) Return after 10-15 minutes and ask the participant to complete the mood scale again.

(3) Arrange to talk to the supervisor. Supervisor will *report to the committee at the conclusion of the study*.

(4) **Administer 3rd mood rating**. Had the participant indicated they are unhappy (levels 8-9), anxious (levels 1-2), or despondent (levels 1-2)? Yes/no

If yes: is this lower than their 1st mood rating? Yes/no

If yes:

(1) Give participants a copy of the PIS, pointing out the PI's contact info.

(2) Invite participants to talk about their concerns or low mood, either to the experimenter (myself) or ring the PI.

(3) Invite the participant to give their phone number, explaining I will ring the next day to check how they are doing.

(4) Ring the participant the next day and check how they are doing. If they are in a low mood that they attribute to the study, suggest that they (i) see their GP, or (ii) ring the PI who will write their GP.

(5) Express gratitude and appreciation for sharing their valuable time in the study.

(6) Ring the participant after 2 weeks. If they are in a low mood that they attribute to the study, suggest that they (i) see their GP, or (ii) ring the PI who will write their GP.

Appendix 3.18: Interview distress policy

Interview distress policy
Participant number _____ Date _____ Experimenter _____

Administer 1st mood rating

Has the interview been cut because the participant became distressed? Yes/no

If yes: Report to supervisor, who will *report to the committee at the conclusion of the study*.

Ask: Comments or questions about the study? How is the participant feeling? Is their mood at normal levels?

Explain: Our policy is not to send participants away from an interview feeling unhappy.

Review:

- If participant feels able to carry on; resume interview/ discussion
- If participant is unable to carry on; go to Administer 2nd mood rating

Administer 2nd mood rating. Had the participant indicated they are unhappy (levels 8-9), anxious (levels 1-2), or despondent (levels 1-2)? Yes/no

If yes: is this lower than their 1st mood rating? Yes/no

If yes:

(1) Ask the participants how they are feeling, listen with empathy.

(2) Return after 10-15 minutes and ask the participant to complete the mood scale again.

(3) Arrange to talk to the supervisor. Supervisor will *report to the committee at the conclusion of the study*.

(4) **Administer 3rd mood rating**. Had the participant indicated they are unhappy (levels 8-9), anxious (levels 1-2), or despondent (levels 1-2)? Yes/no

If yes: is this lower than their 1st mood rating? Yes/no

If yes:

(1) Give participants a copy of the PIS, pointing out the PI's contact info.

(2) Invite participants to talk about their concerns or low mood, either to the experimenter (myself) or ring the PI.

(3) Invite the participant to give their phone number, explaining I will ring the next day to check how they are doing.

(4) Ring the participant the next day and check how they are doing. If they are in a low mood that they attribute to the study, suggest that they (i) see their GP, or (ii) ring the PI who will write their GP.

(5) Express gratitude and appreciation for sharing their valuable time in the study.

(6) Ring the participant after 2 weeks. If they are in a low mood that they attribute to the study, suggest that they (i) see their GP, or (ii) ring the PI who will write their GP.

Appendix 3.19: In process observation poster for Bahrain drug regulatory authority

HELLO!

TO LET YOU KNOW...

OBSERVATION* IS BEING CARRIED OUT IN THIS AREA

THANK YOU ☺

*As part of a study that aims to evaluate the current registration system of herbal medicines (HMs) in the Bahraini National Health Regulatory Authority (NHRA), observation of the registration process is taking place at this area. The observation consist of the researcher observing how herbal products is being registered starting from the initial stage of submission until registration is granted, in order to understand and gain insights of the process. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences at the University of Manchester, UK.

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939].

The researcher has the NHRA permission to conduct the research at the regulatory authority.

If you have any queries about the study then please contact the researcher:

AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK

Appendix 3.20: In process observation poster for Kuwait drug regulatory authority

HELLO!

TO LET YOU KNOW...

OBSERVATION* IS BEING CARRIED OUT IN THIS AREA

THANK YOU ☺

*As part of a study that aims to identify the factors affecting the readiness in the current herbal medicines (HM) registration department in Kuwait to implement proposed recommendations of suitable classification and conformity assessment procedure for HMs registration, observation of the registration process is taking place at this area. The observation consist of the researcher observing how herbal products is being registered starting from the initial stage of submission until registration is granted in order to understand and gain insights of the process. This study forms partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacy and Pharmaceutical Sciences at the University of Manchester, UK.

This project has been approved by the University of Manchester's Research Ethics Committee [2017-1086-3939].

The researcher has the Kuwait Drug and Food Control and Administration (KDFC) permission to conduct the research at the regulatory authority.

If you have any queries about the study then please contact the researcher:

AZHAR ALOSTAD, E-MAIL: AZHAR.ALOSTAD@POSTGRAD.MANCHESTER.AC.UK

Appendix 3.21: Lone working and risk assessment policy

Date:	Assessed by:	Validated by:	Location:	Assessment ref no	Review date:
3/7/2017	Azhar Alostad	Dr Ellen Schafheutle	National Health and Regulatory Authority (NHRA), Bahrain & Kuwait Drug and Food Control and Administration (KDFC), Kuwait	N/A	October 2017 and continued until data collection phase is reached
Task: Conducting research in Bahrain and Kuwait Drug Regulatory Authorities					

Activity	Hazard	Person(s) in danger	Existing measures to control risk	Risk rating	Result
Travelling abroad	Travel routes- by aircraft, car, train	Researcher	• Travel is in daylight on well-used routes. • Arrival is in daylight. • No lone travel after dark.	Low	A

Activity	Hazard	Person(s) in danger	Existing measures to control risk	Risk rating	Result
Lone working in the above sites.	Risk of harm.	Researcher	• A 'buddy' is nominated and given to a colleague – with agreed procedure for contact and escalation plan should contact not be maintained. • A buddy is a responsible person who knows where the researcher is, when they are expected to return, and what action to take if the researcher does not return. • The buddy will have the contact details of the supervisor (and vice versa) prior to the start of the research. The researcher will keep the buddy regularly informed of research activity, and updated about any changes to research activity. • If the researcher does not return as expected, the buddy will attempt to contact the researcher, and then alert supervisor if they fail to establish contact. • Researcher will carry a fully charged mobile phone and map of the area. • The researcher will be prepared to arrange alternative venues for your research activity if security is in doubt. If in doubt of safety or feeling uneasy, the researcher will leave the research site immediately.	Low	N

Activity	Hazard	Person(s) in danger	Existing measures to control risk	Risk rating	Result
Carrying out interviews	Risk of offence.	Researcher	• The researcher has been trained about good interview techniques. • Participant information sheets will explain in layperson's terms what questions might be asked, how long interviews will take and style of interview. • Researchers will behave inconspicuously; avoid making personal remarks about people or environments, and dress appropriately so as to not attract undue attention.	Low	A
Unwelcome or distressing experiences that arise during research.	Risk of distress	Research and research participants	• Where research activities lead to unexpected and unwelcome distressing experiences, researchers will ensure to debrief with supervisor and access sources of support where needed. A distress policy has been piloted for this study. • Any incident that occurs will be reported to the Research Ethics panel so that it can contribute to annual review of the risk management process.	Low	A

Action plan				
Ref no.	Further action required	Action by whom	Action by when	Done
Lone working	Nomination of buddy, details of research plan given to buddy and supervisor contact details exchanged.	Researcher and supervisor	Prior to start of research.	

Notes to accompany General Risk Assessment Form

(1) **Date** : Insert date that assessment form is completed. The assessment must be valid on that day, and subsequent days, unless circumstances change and amendments are necessary.

(2) **Assessed by** : Insert the name and signature of the assessor. For assessments other than very simple ones, the assessor should have attended the University course on risk assessments (link to STDU)

(3) **Validated by** : Insert the name and signature of someone in a position to validate that the assessment has correctly identified hazards and addressed the risks. This will normally be a line manager, supervisor, principal investigator, etc.. who should be competent to identify the hazards and assess the risks. This person should have attended the University's risk assessment course, or equivalent.

(4) **Location** : insert details of the exact location, ie building, floor, room or laboratory etc

(5) **Assessment ref no** : use this to insert any local tracking references used by the school or administrative directorate

(6) **Review date** : insert details of when the assessment will be reviewed as a matter of routine. This might be in 1 year's time, at the end of a short programme of work, or longer period if risks are known to be stable. Note that any assessment must be reviewed if there are any significant changes – to the work activity, the vicinity, the people exposed to the risk, etc

(7) **Task / premises** : insert a brief summary of the task, eg typical office activities such as filing, DSE work, lifting and moving small objects, use of misc electrical equipment. Or, research project [title] involving the use of typical laboratory hardware, including fume cupboards, hot plates, ovens, analysis equipment, flammable solvents, etc.

(8) **Activity** : use the column to describe each separate activity covered by the assessment. The number of rows is unlimited, although how many are used for one assessment will depend on how the task / premises is sub-divided. For laboratory work, activities in one particular lab or for one particular project might include; use of gas cylinders, use of fume cupboard, use of computer or other electrical equipment, use of lab ovens, hot plates or heaters, use of substances hazardous to health, etc

(9) **Hazard** : for each activity, list the hazards. Remember to look at hazards that are not immediately obvious. For example, use of a lathe will require identification of the machine hazards, but also identification of hazards associated with the use of cutting oils (dermatitis), poor lighting, slipping on oil leaks, etc. The same activity might well have several hazards associated with it. Assessment of simple chemical risks (eg use of cleaning chemicals in accordance with the instructions on the bottle) may be recorded here. More complex COSHH assessments eg for laboratory processes, should be recorded on the specific COSHH forms (link).

(10) **Persons in danger** : insert everyone who might be affected by the activity. Remember those who are not immediately involved in the work, including cleaners, young persons on work experience, maintenance contractors, Estates personnel carrying out routine maintenance and other work. Remember also that the risks for different groups will vary. Eg someone who needs to repair a laser may need to expose the beam path

more than users of the laser would do.

(11) **Existing measures to control the risk** : list all measures that already mitigate the risk. Many of these will have been implemented for other reasons, but should nevertheless be recognised as means of controlling risk. For example, restricting access to laboratories or machine rooms for security reasons also controls the risk of unauthorised and unskilled access to dangerous equipment. A standard operating procedure or local rules (eg for work with ionising radiation, lasers or biological hazards) will often address risks. Some specific hazards may require detailed assessments in accordance with specific legislation (eg COSHH, DSEAR, manual handling, DSE work). Where this is the case, and a detailed assessment has already been done in another format, the master risk assessment can simply cross-reference to other documentation. For example, the activity might be use of a carcinogen, the hazard might be exposure to hazardous substances, the existing control measures might all be listed in a COSHH assessment. Controls might also include use of qualified and/or experienced staff who are competent to carry out certain tasks; an action plan might include training requirements for other people who will be carrying out those tasks.

(12) **Risk Rating** : the simplest form of risk assessment is to rate the remaining risk as high, medium or low, depending on how likely the activity is to cause harm and how serious that harm might be.

The risk is **LOW** - if it is most unlikely that harm would arise under the controlled conditions listed, and even if exposure occurred, the injury would be relatively slight.
The risk is **MEDIUM** - if it is more likely that harm might actually occur and the outcome could be more serious (eg some time off work, or a minor physical injury.
The risk is **HIGH** - if injury is likely to arise (eg there have been previous incidents, the situation looks like an accident waiting to happen) and that injury might be serious (broken bones, trip to the hospital, loss of consciousness), or even a fatality.

Schools or administrative directorates may choose to use other rating systems. Typical amongst these are matrices (of 3x3, 4x4, 5x5 or even more complex) which require the assessor to select a numerical rating for both "likelihood that harm will arise" and "severity of that harm". These may give a spurious sense of accuracy and reliability – none are based on quantitative methods. There are methods of estimating risk quantitatively, and these may be appropriate for complex design of load bearing structures and the like. Advice on methods of risk assessment is available from HSS. Whatever system of assessment is adopted, it is **essential** that the assessor has received suitable training and is familiar with the meaning of the terms (or numbers) used.

(13) **Result** : this stage of assessment is often overlooked, but is probably the most important. Assigning a number or rating to a risk does not mean that the risk is necessarily adequately controlled. The options for this column are:

T = trivial risk. Use for very low risk activities to show that you have correctly identified a hazard, but that in the particular circumstances, the risk is insignificant.

A = adequately controlled, no further action necessary. If your control measures lead you to conclude that the risk is low, and that all legislative requirements have been met (and University policies complied with), then insert A in this column.
N = not adequately controlled, actions required. Sometimes, particularly when setting up new procedures or adapting existing processes, the risk assessment might identify that the risk is high or medium when it is capable of being reduced by methods

that are reasonably practicable. In these cases, an action plan is required. The plan should list the actions necessary, who they are to be carried out by, a date for completing the actions, and a signature box for the assessor to sign off that the action(s) has been satisfactorily completed. Some action plans will be complex documents; others may be one or two actions that can be completed with a short timescale.

U = unable to decide. Further information required. Use this designation if the assessor is unable to complete any of the boxes, for any reason. Sometimes, additional information can be obtained readily (eg from equipment or chemicals suppliers, specialist University advisors) but sometimes detailed and prolonged enquiries might be required. Eg is someone is moving a research programme from a research establishment overseas where health and safety legislation is very different from that in the UK.

For T and A results, the assessment is complete.
For N or U results, more work is required before the assessment can be signed off.