ASSESSMENT OF THE REGISTRATION STATUS, AVAILABILITY, UTILIZATION PATTERN AND RATIONALITY OF FIXED DOSE DRUG COMBINATIONS IN NEPAL

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UNIVERSITI SAINS MALAYSIA

APRIL 2010

ASSESSMENT OF THE REGISTRATION STATUS, AVAILABILITY, UTILIZATION PATTERN AND RATIONALITY OF FIXED DOSE DRUG COMBINATIONS IN NEPAL

by

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Thesis submitted in fulfillment of the requirements for the degree of Master of Science

APRIL 2010

DEDICATION

I dedicate this thesis to my grandfather, who passed away just a month before I completed the thesis. The best part of what I've become, I owe to him.

May his soul rest in eternal peace.

ACKNOWLEDGEMENTS

I adore the almighty above for imparting upon me the courage to face the complexities of life and complete this project successfully. This thesis arose in part out of years of research where I worked with a great number of people whose contribution in various ways to the research and the making of the thesis deserved special mention. It is a pleasure to convey my gratitude to them all in my humble acknowledgment.

I would like to express my deep and sincere gratitude to my supervisor, Professor Dr. Mohamed Izham Mohamed Ibrahim, Professor of Social and Administrative Pharmacy, and Deputy Dean of Research and Post Graduate Study at the School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia for his supervision, affection, inspiring advice, encouragement and a constant support. He is an admirable mentor whose excellent supervision and co-ordination made my dissertation work sufficiently commendable. I also thank Associate Professor Dr. Pranaya Mishra, Course Director at Department of Pharmacology, Saba University School of Medicine, Saba, Netherlands-Antilles for co-supervising me in conducting this research work with his valuable suggestion, encouragement and continuous support.

I gratefully acknowledge Dr. Subish Palaian, Post-doctoral candidate at Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia and formerly, Assistant Professor at Department of Pharmacology, Manipal College of Medical Sciences (MCOMS) for his advice, supervision, and crucial contribution, which made him a backbone of this research and so to this thesis. His involvement with his originality has triggered and nourished my intellectual maturity that I will benefit from, for a long time to come. I

also thank Mr. Kadir Alam, Lecturer and Mr. Dinesh Kumar Upadhyay, Assistant Professor at Department of Pharmacology, MCOMS for helping me in the research by several ways. I also thank Associate Professor Dr. Pathiyil Ravi Shankar, Department of Clinical Pharmacology at KIST Medical College, Lalitpur, Nepal for helping me in the research design and support.

My heartfelt gratitude to Mr. Saval Khanal for being my bench mate from long time and listening all my future ideas. Many thanks to Mr. Bhuvan KC, Mr. Jaya Prakash Chalise, Mr. Ram Prasad Bhusal, Mr. Raj Kumar Shah and Mr. Shyam Kumar Mallik for their generous help during the data collection in different cities. Thanks are due to my friends Miss Parbati KC and Miss Sabitri Karki from Charak hospital, Pokhara and Miss Neelima Shrestha from Fishtail hospital, Pokhara for helping me during the data collection of my study. I acknowledge the help of Mr. Bishnu from Batulechaur Health Post for permitting me to carry out the study in health post. I would also like to thank Mr. Rishi Shrestha from the Manipal Teaching Hospital (MTH) for helping me during my study period. Above all, I am indebted to my elite companion Miss Aarati Khanal, who stood beside me and supported me constantly during the study period.

My special thanks to the Health Action International- Asia Pacific (HAI-AP), Colombo, Sri Lanka for funding a part of my research project, ‘The campaign to remove irrational fixed dose combinations’. I am also grateful to the staffs from Department of Drug Administration (DDA), Bijulibazar, Kathmandu for helping me in various assorted ways. Many thanks to the management of MTH for allowing me to work in the Drug Information and Pharmacovigilance Center (DIPC) which helped me

to conduct the research efficiently. I gratefully acknowledge the management of Charak Hospital and Research Center and Fishtail Hospital and Research Center, Pokhara for permitting me to conduct the research in the respective hospitals.

Many thanks go in particular to Prof Dr. Purusotam Basnet, Dean, Faculty of Science and Technology Pokhara University, Pokhara, Nepal and Prof Dr. Natasa Skalko Basnet, Head, Department of Pharmacy, University of Tromso, Norway for their understanding, encouraging and personal guidance and recommending me for further studies.

I extend my sincere thanks to all the faculty members and students from the Discipline of Social and Administrative Pharmacy for their support and help during my data analysis and thesis writing.

Last but not the least; I would like to thank my family. Their constant inspiration and guidance kept me focused and motivated. I am grateful to my dad for giving me the life I ever dreamed. I can’t express my gratitude for my mom in words, whose unconditional love has been my greatest strength. The constant love and support of my sisters is sincerely acknowledged. I cannot forget my maternal uncle, Deepak MAMA, for his decency.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
BP	British Pharmacopoeia
CIMS	Current Index of Medical Specialties
DDA	Department of Drug Administration
DMA	Drug Manufacturing Association
EDL	Essential Drug List
FDC	Fixed Dose drug Combination
GIT	Gastrointestinal Tract
GMP	Good Manufacturing Practice
HAI-AP	Health Action International-Asia Pacific
HP	Health Post
IFDC	Irrational Fixed Dose drug Combination
INRUD	International Network for the Rational Use of Drugs
IP	Indian Pharmacopoeia
JIPMER	Jawaharlal Institute of Postgraduate Medical Education and Research
MIMS	Monthly Index of Medical Specialties
MoH	Ministry of Health
NEDL	National Essential Drug List
NNF	Nepalese National Formulary
NSAIDs	Non-Steroidal Anti Inflammatory Drugs
OPD	Out-Patient Department

OTC	Over The Counter
PHC	Primary Health Care
SHC	Secondary Health Care
SHP	Sub-Health Post
SPC	Summary Product Characteristics
SPSS	Statistical Package for the Social Sciences
STG	Standard Treatment Guidelines
THC	Tertiary Health Care
TUTH	Tribhuvan University Teaching Hospital
UN	United Nations
US	United States
US FDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
VDC	Village Development Committee
WHO	World Health Organization

PENILAIAN STATUS PENDAFTARAN TAHAP SEDIA ADA, CORAK PENGGUNAAN DAN RASIONAL KOMBINASI DRUG BERDOS TETAP DI NEPAL

ABSTRAK

Walaupun kombinasi ubat dengan dos tetap (*Fixed dose drug combinations*) menawarkan kebaikan tertentu dari segi komplian pesakit, kegunaannya menimbulkan banyak persoalan. Penggunaannya di Nepal adalah meluas. Walau bagaimanapun, tidak terdapat kajian yang ekstensif berkaitan kombinasi ubat dengan dos tetap. Kajian ini menilai status pendaftaran, sejauh mana terdapatnya ubat ini, corak dan rasional penggunaannya di Nepal. Pertama, status pendaftaran kombinasi ubat dengan dos tetap dalam senarai ubat kebangsaan dinilai dan sejauh mana terdapatnya ubat ini dalam Formulari Kebangsaan Nepal 1997, Senarai Model WHO bagi Ubat Perlu (edisi ke 15) 2007 dan Senarai Ubat Perlu Nepal (semakan ketiga) 2002 telah dikaji. Kedua, sejauh mana terdapatnya ubat jenis ini yang tidak berdaftar di lima bandar utama di Nepal telah dijalankan menggunakan kaedah persampelan 'snowball' dengan melawat 20 kedai farmasi dalam setiap bandar. Ketiga, kit alat yang telah dibangunkan oleh *Health Action International-Asia Pacific* (*HAI-AP*) telah digunakan untuk memberi justifikasi ubat ini yang diperolehi dari lima bandar di Nepal. Keempat, corak penggunaan ubat ini di institusi penjagaan kesihatan primer, sekunder dan tertiar dari kawasan barat Nepal telah dikaji menggunakan kaedah persampelan sistematik rawak melibatkan 100 preskripsi dari setiap pusat penjagaan kesihatan primer, sekunder dan tertiar. Dapatan kajian mendapati sebanyak 81 kombinasi ubat dengan dos tetap telah didaftarkan di Nepal. Dari jumlah ini, peratusan yang tinggi (66.7%) daripada ubat ini diperolehi dari India. Tujuh peratus dari pada 81 produk terdapat dalam Formulari Kebangsaan Nepal,

6.0% dalam Senarai Ubat Perlu Nepal dan 11.0% dalam Senarai Model WHO bagi Ubat Perlu. Hanya 3 kombinasi hadir dalam semua formulari dan senarai ubat. Sebanyak 41 ubat tidak berdaftar diperolehi dari lima bandar. Tidak ada satupun kombinasi ubat dengan dos tetap memenuhi kesemua keperluan fundamental sepertimana yang telah ditetapkan dalam kit alat. Ini dapat diklasifikasikan sebagai tidak rasional. Dalam pusat penjagaan kesihatan primer, 206 ubat telah dipreskripsikan dan 20.0% daripadanya adalah kombinasi ubat dengan dos tetap. Ubat yang paling banyak dipreskripsikan adalah agen antimikrobial (57.1%). Kos harga unit kesemua ubat adalah di bawah 100 NR (USD1=NR80). Dalam pusat penjagaan sekunder, sebanyak 309 ubat telah dipreskripsikan dan 30.0% adalah kombinasi ubat dengan dos tetap. Jenis kombinasi ubat dengan dos tetap yang paling banyak dipreskripsikan adalah vitamin, mineral dan makanan tambahan (25.8%). Peratusan ubat dengan kos di bawah 100 NR adalah 63.5%. Bagi pusat penjagaan kesihatan tertiar pula, 33.7% daripada 270 ubat yang telah dipreskripsikan adalah kombinasi ubat dengan dos tetap. Sepertimana di pusat penjagaan kesihatan sekunder, jenis kombinasi ubat dengan dos tetap yang paling banyak dipreskripsikan di pusat penjagaan kesihatan tertiar ini adalah vitamin, mineral dan makanan tambahan (40.6%). Peratusan ubat dengan kos di bawah 100 NR adalah 50.5%. Sebagai kesimpulan, kajian ini mendapati banyak kombinasi ubat dengan dos tetap telah didaftarkan di Nepal. Penggunaan yang agak ekstensif didapati di berbagai tahap pusat penjagaan kesihatan, di samping terdapatnya ubat yang tidak didaftarkan serta tidak rasional dalam pasaran farmaseutikal Nepal yang perlu dikeluarkan.

ASSESSMENT OF THE REGISTRATION STATUS, AVAILABILITY, UTILIZATION PATTERN AND RATIONALITY OF FIXED DOSE DRUG COMBINATIONS IN NEPAL

ABSTRACT

Fixed dose drug combinations (FDCs), though offer certain advantage in terms of patient compliance, their use is highly debatable. There is a widespread use of FDCs in Nepal. However, there are no extensive studies on FDCs. The present study evaluated the registration status, availability, utilization pattern and rationality of FDCs in Nepal. Firstly, registration status of FDCs in the national drug list was assessed and their availability in the Nepalese National Formulary (NNF) 1997, the WHO Model List of Essential medicines (15^{th} Edition) 2007 and the Essential Drug List (EDL) of Nepal (third revision) 2002 were analyzed. Secondly, the availability of un-registered FDCs in five major cities of Nepal was carried out using a snowball sampling method with a visit of 20 retail pharmacies from each city. Thirdly, the toolkit developed by Health Action International-Asia Pacific (HAI-AP) was used to justify the rationality of the FDCs obtained from the five cities of Nepal. Fourthly, the utilization pattern of FDCs in primary health care (PHC), secondary health care (SHC) and tertiary health care (THC) centers from western Nepal was evaluated using systematic random sampling method involving 100 prescriptions from each health care center. A total of 81 FDCs were registered in Nepal. Higher percent (66.7%) of FDCs were from India. Among the total 81 FDCs only, 7.0% were present in the NNF, 6.0% in the EDL of Nepal and 11.0% in the WHO Model List. Only three combinations were present in all the formularies and drug lists. Altogether, 41 un-registered FDCs were obtained from the five cities. None of the FDCs fulfilled all the fundamental requirements as stated in the toolkit, thus

categorizing them to be ‘irrational’. In the PHC center, 206 drugs were prescribed among which 20.0% were FDCs. Antimicrobials were the highly prescribed FDCs (57.1%). The unit price costs of all FDCs were below 100 NRs (USD1=NRs 80). In the SHC center, 309 drugs were prescribed out of which 30% were FDCs. Vitamins, minerals and dietary supplements were highly prescribed FDCs (25.8%). The costs of 63.5% of FDCs were below 100 NRs. In case of THC center, 33.5% were FDCs out of total 270 drugs prescribed. As in SHC center, vitamins, minerals and dietary supplements were highly prescribed FDCs (40.6%). The costs of 50.5% of FDCs were below 100 NRs. In conclusion, considerable amount of FDCs are registered in Nepal with extensive utilization in different levels of health care centers along with the availability of unregistered and irrational FDCs in Nepalese pharmaceutical market which needs to be weeded out.

CHAPTER ONE

GENERAL INTRODUCTION

1.0 Introduction

1.1 Background

The basic aim of pharmacotherapy is to treat a particular ailment with effective, safe and good quality medicines. Large proportions of the available drugs are of little importance in terms of essential and basic health care. There is no doubt that all the medicinal preparations are meant for the treatment of ailments and diseases, out of which only a few drugs are lifesaving and essential; rest of the drugs are substitutes for others (Sreedhar *et al.*, 2006). Combination products which are also known as 'fixed dose drug combinations' (FDCs) are combination of two or more active ingredients in a single pharmaceutical dosage form (Gautam and Saha, 2008). The United States Food and Drug Administration (US FDA) defines a combination product as a 'product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product' (Combination product definition 2007). The term 'fixed-dose combination product' is synonymous with 'fixed-ratio combination product'. Both terms refer to a product that contains two or more active ingredients. Since the product is of defined composition, the two (or more) ingredients are present in a fixed ratio. Hence, the term 'fixed dose' or 'fixed ratio' combination is used (Regulation of fixed-dose combination products 2003). The availability, marketing, utilization pattern and rationality of FDCs are becoming increasingly important from a public health perspective.

Combination therapy has been used since therapeutics was first practiced (Lyons and Petrucelli, 1987). Due to many reasons the use of FDCs are very common worldwide although many drugs are excellent when mingled and many are fatal (Manson and Routledge, 2005). It has become a very common practice for the physicians to prescribe polypharmacy. Though prescribed widely, the benefits of FDCs is debatable (Avijit, 2007). Many pharmacies demonstrate the popularity of FDCs over-the-counter (OTC) preparations, and more than one third of all new drug products introduced worldwide in 1978 were combination products or preparations, although there is an interesting variation between countries such as 10% in Japan to 56% in Spain (Helfand, 1979).

There are several advantages and disadvantages of FDCs. Potential advantages include: increased convenience for prescribers and patients, claimed to have a better patient compliance, considered to be cheaper as compared to a single product, logistics including procurement and distribution is easy (especially in the remote areas). Potential disadvantages include: inflexible fixed dose ratio, incompatible pharmacokinetics, increased toxicity, and physician and pharmacist ignorance of content, and increased chance of adverse drug reactions (ADRs) and drug interactions, encourage polypharmacy, drug resistance, some FDCs lead to abuse etc. (McMahan, 1975; Poudel *et al.*, 2008b; Shenfield, 1982). Although the existed FDCs possess several advantages and disadvantages, their availability is still skeptical. Whether the pharmaceutical companies make these FDCs because of the demand of the physicians or physicians prescribe multiple drugs because these dosage forms are easily available is a highly debatable issue (Avijit, 2007).

Nepal is a landlocked country surrounded by India on three sides and China in the north. Its shape is roughly rectangular, about 850 kilometers long and about

200 kilometers wide, and comprises a total of 147 181 square kilometers of land. Nepal commonly is divided into three broad physiographic areas: 'the Mountain Region', 'the Hilly Region', and 'the Terai Region' also known as the 'plain region' and divided into five development regions: Eastern, Central, Western, Mid Western and Far Western region. Kathmandu is the capital city and is located in the Central development region. The health system at national level consists of the Ministry of Health (MoH), Department of Health Services with its various divisions and units. Generally, the health care status of Nepalese population is poor. Health-care problems were varied and enormous. Poor health conditions were evident in the high rate of infant mortality- 48 per 1000 live births (2005), a short life expectancy at birth- 61 years (2004) and high maternal mortality- 281 per 10 000 live births (2006) (Nepal Health System Profile, 2007). There was no doubt that considerable progress has been made in health care, but the available facilities were still inadequate to meet the growing medical needs of the population. The preventive, curative, and promotive health services have been provided through 74 hospitals, 17 health centers, 79 primary health centers, 765 health posts and 2 588 sub-health posts, and 47 950 community level health workers (Financing Drugs In South East Asia, 1996). The annual medicine consumption is over 3719.3 million Nepalese rupees (approximately US$ 46 million), with an estimated 28.5% rate of increase in consumption every year (Quantification of Drug Consumption in Nepal, 2006). Nepalese domestic pharmaceutical companies manufacture only 35.4% of medicines consumed in Nepal; rest is imported from foreign countries (Quantification of Drug Consumption in Nepal, 2006). The Department of Drug Administration (DDA) is a drug regulating body of Nepal. DDA regulates the import, export, procurement, sales, and manufacturing of the drug in the country.

1.2 Problem statement

Many of the FDCs are harmful and a vast majority of them are irrational. The 15th edition of WHO Model List of Essential Drugs contains 25 FDCs out of 352 medicines in total (Poudel *et al.*, 2008). The third revision of National Essential Drug list of Nepal (NEDL) contains 14 FDCs. Although, only a handful of essential FDC have been recognized by World Health Organization (WHO) and National Essential Drug List of Nepal, a wider variety of FDCs are available in the market today. Some FDCs increase the risk of side effects, lead to an ineffective dosage which are liable to abuse with potential for drug resistance and may also needlessly increase cost with reduction in quality of drug therapy (Beardshaw, 1983). FDCs are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in its therapeutic effects, safety or compliance. Because of the deficiency of a clear, comprehensive and rational drug policy and also lack of clear statement on the production and registration of FDCs, the irrational FDCs are booming in the market (Poudel *et al.*, 2008b; Patel *et al.*, 2005). Often there is a competition among the drug companies to promote doctors to prescribe branded medicines in exchange for slight favors. Such practice results in unnecessary prescription of drugs and combinations that are irrational including many irrational FDCs (Patel *et al.*, 2005).

No doubt that FDCs are popular among both patients and doctors, but always the reason behind this is not clear. On one hand physicians defend their right to prescribe FDCs (Davies and Wilson, 1975) and on the other hand regulatory authorities attempt to stop or restrict their use (Crout, 1975). Supporters of FDCs argue that the USFDA and WHO reports are made by bureaucrats and such

academicians who never treat patients and are not in direct contact with patients. According to them, they believe that drug companies have made adequate market research and they claim that patients readily take such drugs and that they must be effective or else they won't be so popular (Budd, 1975). On the other hand, those who oppose to the concept of FDCs, argue that such preparations have little significance and a lot of dangers. According to them higher number of FDCs simply reflects public ignorance, lack of pharmacological knowledge by prescribers. They suggest that the marketing of such FDCs is based on a false philosophy that 'if one is good, two is better, and three best of all' (Shenfield, 1982). Studies from developing countries like Nepal have identified the use of FDCs in different health care settings (Joshi *et al.*, 1997; Sarkar *et al.*, 2004a; Rauniar *et al.*, 2003). These studies are only preliminary and do not extensively study the FDCs. Moreover, there is no extensive study in Nepal on the availability, utilization pattern and rationality of FDCs.

1.3 Literature review

A FDC refers to the combination of two or more drugs in a single pharmaceutical formulation. Rational FDCs can be of immense help to the health care system which may improve the quality of life for many. Meanwhile, irrational FDCs increase the risk of ADRs, lead to an ineffective dosages, and ultimately increases cost. In many cases their stability is doubtful, reducing the efficacy of many preparations. Several studies and papers in the literature indicate that FDCs are commonly utilized and prescribed in different health care centers in both developed and developing countries. FDCs are utilized as OTC to the prescription medicines in different health care centers. There are very few studies carried out in

these issues. Although there are very limited studies done in these areas, in this section we will try to review some of the published studies which are relevant to our objectives.

1.3.1 Literature on registration status of fixed dose drug combinations

All the drugs that are registered in a country are for the prevention and treatment of diseases. In many countries, the drug production, distribution and registration is monitored by the drug controlling regulatory. There are some of the studies on requirements for combined pharmaceutical preparations but we were not able to assess the studies focusing specially on FDCs.

A comparison of the list of FDC therapies used in the USA, UK and Israel was carried out by Cohen *et al.*, (2001). They counted the total list of drugs and FDC drugs manually from a list of generic names registered in the countries. They also counted the number of drugs in four characteristic subgroups: cardiovascular, anti-infective, gastrointestinal, and dermatological. Data for drugs in the USA, UK and Israel were taken from the Physician's Desk Reference (PDR 1997), the British National Formulary (BNF March 1997) and the Monthly Ethical Drug Indexed Compilation (MEDIC July 1997), respectively. FDC drugs in the USA and UK was higher than in Israel (20%, 25% and 15% respectively) and they found a similar trend was found in all subclasses of FDC drugs except for the anti-infective category in which the percentage of FDC drugs was low and similar in all countries. The list of FDC drugs varies greatly between the USA, UK and Israel, reflecting the differences in the outcome of debate between the pharmaceutical companies and the regulatory authorities.

1.3.2 Literature on availability of unregistered fixed dose drug combinations

A study by Poudel *et al.,* (2008) from Nepal found that several unregistered FDCs are available in the pharmaceutical market and many of them were irrational. Although the study found the unregistered FDCs but the authors did not mention the reason behind their irrationality. It was a preliminary study which sensitized the issue to the regulatory authority.

Gautam and Aditya, (2006) found that Current Index of Medical Specialties (CIMS) and Monthly Index of Medical Specialties (MIMS), widely used by health care professionals list more than 100 IFDCs which are not approved in any developed countries but are being marketed in developing countries like Nepal and India.

1.3.3 Literature on rationality of fixed dose drug combinations

Although some studies conclude that FDCs are registered and available in the country, they could not justify the rationality of the particular FDC. During our literature survey we could not come across studies mentioning a particular FDC as either 'rational' or 'irrational'.

1.3.4 Literature on utilization pattern of fixed dose drug combinations

A study from Ireland examined the prescribing pattern of the paracetamol-containing analgesics in primary care (Usher *et al.,* 2005). A national primary care prescribing database was used to investigate patterns of usage. Twenty-six thousand three hundred and eighteen patients who were new to therapy with paracetamol and paracetamol-containing analgesics between January and June 2002 were identified. FDC of paracetamol and dextropropoxyphene was the most commonly prescribed

analgesic, accounting for 42% of all prescriptions. Paracetamol-containing combination analgesics are widely prescribed but the use of FDC of paracetamol and dextropropoxyphene is particularly controversial. The results may indicate inappropriate use in primary care and suggest the need for educational programs highlighting the relative benefits and risks of use of such combination analgesics. Several analgesic preparations containing paracetamol and an opioid (such as codeine or dextropropoxyphene) available either via prescription only or for self-medication via over-the-counter availability (such as FDC of paracetamol and ibuprofen) need to be justified as rational combinations. It requires further research since it has been reported that such combinations offers no substantial advantages in terms of safety and efficacy.

Pan *et al.*, (2008) from the USA investigated the impact of FDC on adherence to prescription medications. Longitudinal data from a large claims database were used to assess adherence for one year. Authors found that the FDC enhanced adherence rates by approximately 13% when compared to a 2-pill regimen. But there are certain areas of controversy in the study. Only short term effects were measured. The generalizability of these results is limited. The study population included well-insured employees of large companies. Future studies may need to focus on individuals with less generous prescription drug coverage. Also, no information was available on length or severity of disease.

A retrospective study from a tertiary hospital in Nepal by Sarkar, and Das, (2000) analyzed the prescribing trend of different FDCs. An audit of the prescriptions revealed that 40% of the prescriptions contained FDCs however; FDCs in accordance with recommended DDA, Ministry of Health and WHO lists of FDCs were only 0.8% and 2.1%, respectively. The most commonly prescribed FDCs not

having any rational basis were multivitamins, cough and cold remedies and antimicrobials which constitute nearly 63% of total FDCs prescribed. Nearly 98% and 95% of the FDCs prescribed did not confirm to the recommended Nepal and WHO lists of FDCs, respectively. The study was able to address the scenario of FDCs utilization pattern in tertiary hospital but there were some controversies in the study. The authors concluded that although the FDCs are not included in the WHO list of FDC's but meet certain criteria to be justified as rational, they should be designated as justified and rational FDC. So, a critical reappraisal is required and consensus should be attained at the scientific forums and regulatory authorities.

Sarkar *et al.,* (2004) analyzed the analgesic use in dentistry in a tertiary hospital in Western Nepal. A total of 1820 prescriptions were analyzed where the total analgesics prescribed were 1358 that account for 36.7% of total drugs prescribed. A total of 38.9% analgesics were fixed-dose combinations (FDCs) of two drugs and the most common analgesic combination used was 'ibuprofen and paracetamol' and 'paracetamol and opioid analgesics'. All opioid analgesics were prescribed in combination with paracetamol. But the authors couldn't justify the rationality of this combination drugs although they mentioned that it is best to avoid combination therapy with more than one non-opioid analgesic as there is little evidence of extra benefit to the patient and the incidence of side effects generally is additive. The issue is burning in developing countries like Nepal. The rationality behind the combination of NSAIDs should be justified which needs a further research in this area.

Another similar study by Das *et al.,* (2003) evaluated drug use pattern during pregnancy in a teaching hospital in Western Nepal. Random collection of 2156 prescriptions of pregnant women from the antenatal care in obstetrics Out-Patient

Department (OPD) at Manipal Teaching Hospital (MTH), Nepal was done. The average number of drugs per prescriptions was found to be 2 with 64.8% of drugs prescribed in the form of FDCs. Ideally, a woman should minimize taking drugs as soon as she plans to become pregnant or, when she suspects that she might be pregnant but according to this study the use of FDCs was rampant. These issues require further research and findings because only little information is available for the teratogenic potential of most FDCs (prescription as well as over-the-counter drugs).

A prospective study by Rauniar and Naga, (2003) analyzed a total of 467 prescriptions collected from the inpatients of major specialties in a tertiary care teaching hospital, Nepal. Out of total 467 prescriptions, 206 (44.11%) prescriptions contained 276 FDC with a mean of 0.5 per prescription. Most commonly used FDCs were multivitamins (56.15%), analgesic (27.89%), antimicrobials (7.95%), antacids (3.98%) and cough mixtures (3.62%). The authors mentioned about the use of some irrational FDCs but they couldn't justify on what basis they considered those FDCs as 'irrational' in the study.

Another study identified the drug prescribing practice of dentists in a tertiary care teaching hospital in western Nepal (Sarkar *et al.*, 2004 b). A total of 1820 prescriptions of dental patients were collected by a random once weekly survey. The information was compiled, scored and analyzed in consultation with dentists using WHO guidelines. The average number of drugs prescribed was 2.03 and 38% drugs were fixed dose combinations of two or more drugs.

A cross-sectional, descriptive study by Alam *et al.*, (2006) teaching hospital in western Nepal analyzed the prescription of out-patients for rational prescribing and dispensing and evaluated the patient's knowledge regarding use of drugs, using

INRUD indicators. A total of 247 prescriptions were randomly selected for analysis, where 720 drugs were prescribed. Among the total, 21.7% of the total drugs consisted of FDCs, only 40% of drugs were from the Essential Drug List of Nepal and 29.44% were from the WHO Essential Drug List. Authors found that more than half (54.17%) of the drugs were from Nepalese National Formulary and 35.69% were from WHO Model Formulary. Dermatological products were most commonly prescribed followed by drugs acting on central nervous system, antimicrobials and drugs acting on cardiovascular system. The study had some limitations. It was conducted for a short period of time with limited sample size and seasonal variation was not evaluated.

A retrospective study on prescribing patterns for 100 randomly selected geriatric patients admitted over a period of one year to the medical wards of the Tribhuvan University Teaching Hospital (TUTH) in Nepal showed that the incidence of polypharmacy and FDCs was prevalent (Joshi *et al.,* 1997). Authors found that during a hospital stay, 73% patients received more than five, 54% received more than eight, and 24% received more than nine drugs concurrently. Among the total drugs prescribed 15.4% drugs was FDCs. Relatively small number of patients in the study was observed as a limitation which made it difficult to directly extrapolate the findings to other hospitals.

Lamichhane *et al.,* (2006) evaluated the morbidity profile and prescribing patterns among the outpatients in a teaching hospital in Western Nepal through a one year retrospective hospital record based study. Altogether, 1261 cases were analyzed. The mean number of drugs was 1.99. Authors found that only 19.5% and 39.6% of drugs were prescribed by generic name and from the Essential Drug List. Antibiotics were found to be commonly prescribed group of drugs. The most

commonly prescribed FDC antibiotics were 'Amoxicillin and Cloxacillin'. The controversy in the study was found to be the use of this FDC of amoxicillin and cloxacillin. The FDC of ampicllin and cloxacillin often does not contain the requisite amount of each individual antibiotic. The combination is not synergistic as cloxacillin is not active against gram negative bacteria and does not inhibit beta lactamase while ampicillin is not active against staphylococci. Thus, the combination only adds to the cost and adverse effects of both drugs of the combination preparations, 19.6% of preparations contained at least one NSAID, 6.4% of preparations contained at least one antibiotic while 5.5% of preparations contained at least one corticosteroid. Some of the drug combinations being used were irrational. Prescriber education may be helpful in encouraging rational prescribing.

1.4 Rationale of the study

Only a few drugs that are available in a Nepalese pharmaceutical market are life saving and essential (Poudel *et al.*, 2008b) the remaining are substitutes or alternative for others with around 65% of the medicines being imported from foreign countries and only around 1/3rd being manufactured by domestic companies (Quantification of Drug Consumption in Nepal, 2006). For every drug to be registered in Nepal it should pass through the guidelines prepared by the drug regulatory authority (DDA) of Nepal. The DDA was established in the year 1979 after the promulgation of Drug Act 1978, an act made for the regulation of drugs so as to prohibit the misuse or abuse of drugs and allied pharmaceutical materials as well as the false or misleading information relating to efficacy and use of drugs and to regulate and control the production, marketing, distribution, export-import,

storage and utilization of those drugs which are not safe for the use of the people, efficacious and of standard quality (Drug Act 2035 BS, 1978).

Since past, the DDA has banned several medications for production, sale-distribution and import in order to ensure safe use of medicines in Nepal. Few combination products such as FDCs of amidopyrin, phenacetin, clioquinol, combination containing two or more antihistamines, combination of antacid with vitamins or anti-inflammatory drugs and many more were banned (Official website of the department of drug administration, 2008). Although, the DDA have initiated some of the activities for banning these irrational combinations, they did not address the effective guidelines on the registration of the FDCs.

Many FDCs are available in the Nepalese pharmaceutical market which is not listed in the drug list of Nepal (Poudel *et al.,* 2008). Moreover, these combinations are available as Over The Counter (OTC) without a prescription. Many of these FDCs are considered to be irrational and are particularly prevalent in the plain lands of Nepal which is bordered with India. Studies from Nepal also concluded that there is an extensive utilization of FDCs in different health care settings (Lamichhane *et al.,* 2006; Sarkar & Das, 2000). These FDCs are available for the treatment of various aliments ranging from nutritional deficiency to cardiovascular diseases (Poudel *et al.,* 2008b).

Since, these FDCs are available and are extensively utilized in Nepal, they need to be categorized as 'rational' or 'irrational' based on the availability of scientific evidences and literatures. Health Action International-Asia Pacific (HAI-AP) an independent global network that is working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy recently developed a toolkit to identify irrational FDCs (IFDCs).

This toolkit can be used as a standard reference to categorize a FDC as 'rational' or 'irrational' (HAIAP, Advocacy and campaigns to remove irrational fixed dose combinations, 2008).

1.5 Research questions

The overall study had the following research questions:

a) Are all fixed dose drug combinations registered in Nepal and listed in different drug list and formularies of Nepal?

b) To what extent do the unregistered fixed dose drug combinations available in Nepal?

c) Are the unregistered fixed dose drug combinations which are available in Nepal rational?

d) How are fixed dose drug combinations utilized in different levels of health care centers in Nepal?

1.6 Study objectives

The present study was conducted based on the following general and specific objectives:

General objective: To evaluate the registration status, availability, utilization pattern and rationality of fixed dose drug combinations (FDCs) in Nepal.

Specific objectives:

a. To identify the registration status of all fixed dose drug combinations and their presence in informational formularies and drug lists in Nepal

b. To carry out the market survey to assess the extent of availability of fixed dose drug combinations that are not registered in Nepal

c. To evaluate the rationality of the various unregistered fixed dose drug combinations found from the market survey.

d. To evaluate the utilization pattern of fixed dose drug combinations in primary, secondary and tertiary health care centers in Western Nepal.

1.7 Significance of the study

Research in these areas may also act as a cornerstone for a government to implement policy issues in use of FDCs as well as setting up criteria for the manufacturing and registering FDCs in particular countries. In Nepal, as such there are no such studies which have evaluated the registration status, availability and utilization status of FDCs in different health care settings. This study may act as a standard or as a reference for further researches in this area. Many researches are needed in these issues since several questions have not been answered in these areas.

CHAPTER TWO

EVALUATION OF THE REGISTRATION STATUS OF FIXED DOSE DRUG COMBINATIONS IN NEPAL

2.1 Introduction

2.1.1 Background

The main objective of the pharmaceutical policy of the vast majority of the countries is to ensure the access to essential, quality, effective and safe drugs, and that these drugs are used rationally. It is the responsibility of the government regulatory bodies through their national regulatory systems to assure that all drugs met criteria for quality, efficacy and safety. Internationally, it is accepted that drug production and distribution require regulatory approval and supervision. These activities are divided into three components: a) product registration, including authorization for the marketing of drugs and monitoring of their efficacy and post marketing safety; b) regulation of drug production, importation, and distribution; and c) regulation of drug marketing and drug information (WHO medicines strategy, 2004-2007; WHO, The world medicines situation, 2004). For a drug product to be registered in Nepal, several documents need to be submitted through the authorized Nepalese importer which contains information on detail formulation including recipients, color, flavor, product specification, methods of analysis, samples of the product (2-unit pack), labels and package, analytical reports, and many more (Requirements for Registration of Modern Medicines, 1981). For registering the new FDC and new molecule previously not registered in Nepal and or not included in recognized Pharmacopoeias, following information are required: a) Summary of

Product Characteristics (SPC); b) Name of the country, where the drug is marketed; c) Where and when the drug had been introduced in the home country; d) List of the other drugs having similar indication which are already marketed. If the new product fulfills the above mentioned criteria then they are registered in the Ministry of Health, DDA, Nepal (Registered drug products, 2008).

The Ministry of Health of Nepal in association with DDA published a formulary for the first time in the year 1997 as Nepalese National Formulary (NNF). The idea behind bringing the formulary was to identify the drug products needed for the country according to disease prevalence. NNF provides information on drugs and their dosage forms available in the country, with special emphasis on the essential drugs. It contains guidance on rational prescribing, classified notes on drugs, formulary based on the dosage forms and strength described in pharmacopoeias etc. (Nepalese National Formulary, 1997)

National List of Essential Drugs (NEDL) in Nepal was first published in 1986. The list was revised in 1992, 1997 and 2002 [(National list of essential drugs Nepal (third revision), 2002)]. The fourth revision is under progress. Essential medicines are those that satisfy the priority health care needs of the population and are selected with due regard to disease prevalence, evidence on safety and efficacy, and comparative cost-effectiveness (Hogerzeil, 2004). Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at price the individual and the community can afford. (National List of Essential Drugs, fourth revision, 2009). Medicines are categorized as main and complementary in the national list. The complementary list represents essential

medicines for priority diseases, for which specialist medical care and/or specialist training and specialized diagnostic or monitoring facilities are required.

The WHO Model List of Essential Medicines has been widely adopted or adapted in over 150 countries (Essential Medicines, 2006). Large number of problems are associated with the utilization of therapeutic drugs in developing countries; inadequate access to cost effective drugs, poor procurement, poor management and distribution, irrational prescription and consumption. In response to these problems, the essential drug concept was introduced by WHO in the year 1977 (Mandani & Walker, 1986). The 15th Edition of the Model List is divided into two parts which consist of the core list and the complementary list. The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. Similarly, the complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed (WHO Model List of Essential Medicines 15th List, 2007). The compilation of an essential medicines list enables health authorities, especially in developing countries, to optimize pharmaceutical resources.

2.1.2 Problem statement

In developing countries like Nepal it is evident that the use of pharmaceuticals is not justified medically and economically (Jha *et al.*, 2009). Both in the public and private sectors medicines and pharmaceuticals are often managed and used inefficiently and irrationally. This may be due to several reasons, but one

of the dominating factors may be the poor selection of medicines and not prescribing in accordance with the standard treatment and other guidelines (Holloway and Green, 2003). Those who are involved in the health sector decision making and the selection of drugs for the national health care objective must be concerned with the issues of irrational prescribing and cost effectiveness of the drug selected for as the essential drug for the particular countries. According to the fifteenth WHO Model List of essential medicines (March 2007), only 25 drug combinations are listed (approved). The latest version of the NEDL of Nepal approved only few FDCs (Poudel *et al.*, 2008b). The FDCs account for 7% of the total drugs in the essential medicine list, whereas in Nepal a number of irrational drug combinations are easily available and can be bought without necessarily presenting a prescription (Official website of the DDA 2008; Gautam and Aditya, 2006). Meanwhile there are no any strict guidelines on registration of FDCs in Nepal.

2.1.3 Rationale of the study

Registered drug list of Nepal contains the list of drug products with manufacturers including ingredients. It contains allopathic as well as ayurvedic preparations together with the price of each product. For a particular product to be registered in Nepal, it needs to pass through several measures. They should meet the criteria set up by the DDA. Considerable amount of FDCs are registered in drug list of Nepal. Selections of essential drugs are based on the aim to promote the rational use of medicines and ensure the availability of good quality medicines and economic brands. The presence of FDCs in the Essential Drug List of Nepal and NNF needs to be analyzed.

Prescribing doctors and health care professionals must be aware of the concept of Essential Drug List and formularies like NNF so as to promote rational prescribing and to eliminate the unnecessary use of several irrational drug combinations. A study covering five districts in Nepal revealed that 54% of clinical facility staff were not aware of the Essential Drug List (EDL) and 88% were not aware of the Standard Treatment Guidelines (STG) (Blum, 2002). Analyzing the registration status and the presence of FDCs in different drug list and informational formularies helps the utilization of rational FDCs which in turn aid in weeding out the irrational combinations booming in the pharmaceutical market. The study is carried out for the first time in Nepal so the findings may also be beneficial for the appropriate policy changes.

2.1.4 Study objectives

This part of the study had the following research objectives:

2.1.4.1 General objective

The general objective of the study was to evaluate the legality and registration status of the fixed dose drug combinations in the drug regulatory authority of Nepal.

2.1.4.2 Specific objectives

The various specific objectives of the present study are as follows:

1. To evaluate the registration status of fixed dose drug combinations in the national drug list of Nepal.

2. To evaluate the availability of fixed dose drug combinations in Nepalese National Formulary (NNF) 1997, WHO Model List of Essential Medicines (15th Edition) 2007 and Essential Drug List of Nepal (third revision) 2002.

3. To evaluate the therapeutic class of the fixed dose drug combinations registered in Nepal.

2.2 Methodology

2.2.1 Study design

Cross-sectional observational study evaluating the registration status of the fixed dose drug combinations in the drug list of Nepal and to evaluate their presence in informational formularies and drug lists.

2.2.2 Inclusion and exclusion criteria

All the FDCs that are registered in the drug list of Nepal were included in the study. Several brands of same generic were considered as one FDC. For example, there were several brands of FDCs of paracetamol and ibuprofen in different strengths but considered it as a single FDC. FDCs of topical, intravenous and ayurvedic preparations were excluded from the study. The topical preparations contain drug combinations in indefinite doses so it will be almost impossible to categorize as either 'rational' or 'irrational' while the ayurvedic preparations usually don't have any scientific justification for their efficacy. So, these preparations were excluded from the study.

2.2.3 Study tools

The various tools used in the study are as follows:

i. Drug list of Nepal: The drug list of Nepal contains all the registered drug products along with the list of manufacturer including the ingredients. The drug list was obtained from the DDA through communications with the staff in the DDA. The drug list used in our study was updated till March 2008.

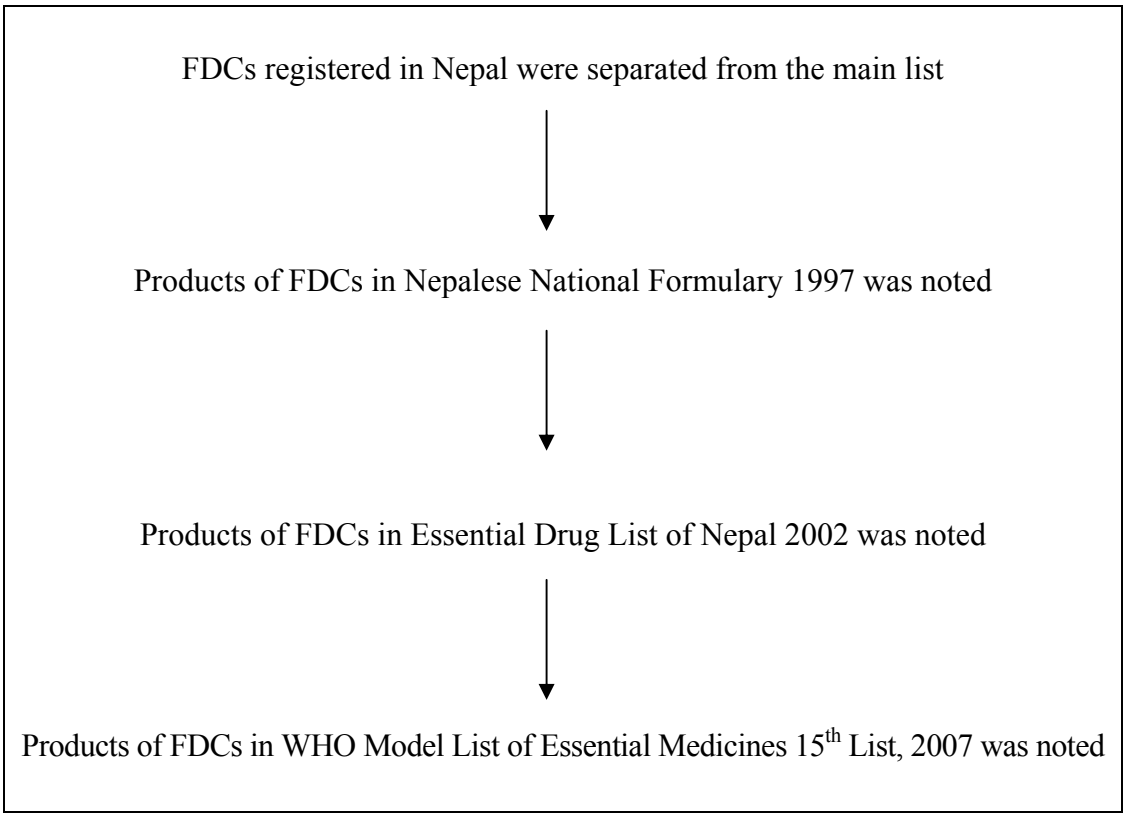
ii. Nepalese National Formulary (NNF), 1997: NNF provides information on drugs and their dosage forms available in the country, with special emphasis on the essential drugs. It contains guidance on rational prescribing, classified notes on drugs, formulary based on the dosage forms and strength described in pharmacopoeias etc. The idea behind the publication of NNF was to identify the products needed for the country according to the diseases prevalence. A detailed list of drug interaction is also included in the formulary.

iii. National list of essential drugs Nepal (third revision) 2002: National List of Essential Drugs was first published in 1986. The list was revised in 1992, 1997 and 2002. It contains the list of drugs considered to be essential for Nepal. They are selected considering the disease prevalence, evidence on safety and efficacy, and comparative cost-effectiveness.

iv. WHO Model List of Essential Medicines 15th List, 2007: The 15th Edition of the Model List is divided into two parts which consist of the core list and the complementary list.

2.2.4 Modality of operation

The registered drug list and the Nepalese National Formulary, 1997 was obtained from the Ministry of Health (MoH), Department of Drug Administration. The Essential Drug List of Nepal and the WHO Model List of essential medicines were obtained online through the internet and the below mentioned procedure was followed.



Following this, a therapeutic classification of FDCs registered in Nepal was carried out. Finally the country of origin of FDCs that were registered in Nepal was analyzed.

2.3 Results

A total of 81 FDCs were registered in Nepal at the time of March 2008. These 81 FDCs were further evaluated based on the study objectives.

2.3.1 Fixed dose drug combinations registered in Nepal

Among the total 42 manufacturers of FDCs, 66.7% (n= 28) of manufacturers were from India followed by 31.0% (n= 13) of manufacturers were from Nepal. The details are shown in Table 2.1.

Table 2.1 Country of origin of fixed dose drug combinations registered in Nepal (n=42)

Country of origin	Frequency	Percentage
India	28	66.7
Nepal	13	31.0
Bangladesh	1	2.3

2.3.2 Availability of fixed dose drug combinations in Nepalese National Formulary (NNF) 1997, WHO Model List of Essential Medicines (15th Edition) 2007 and Essential Drug List of Nepal (third revision) 2002

Among the total 81 FDCs registered in Nepal, only 7.0% (n= 6) were present in NNF, 6.0% (n= 5) were present in Essential Drug List of Nepal (3rd Revision 2002) and 11.0% (n= 9) were present in WHO Model List of Essential medicines (15th Edition). Only three combinations; the combination of sulphamethoxazole and trimethoprim, the combination of pyrimethamine and sulfadoxine and the combination of ferrous sulphate and folic acid were present in all the formularies and drug lists. The details regarding the registration status of FDCs are shown in Table 2.2.

Table 2.2 Availability of fixed dose drug combinations in different informational formularies and drug lists (n= 81)

S. No	Fixed dose drug combinations	Incidence in		
		Nepalese National Formulary (NNF, 1997)	Essential Drug List of Nepal (3rd Revision 2002)	WHO Model List of Essential Medicines (15th Edition, 2007)
1.	Diloxanide Furoate+ Metronidazole	✓	X	X
2.	Sulphamethoxazole + Trimethoprim	✓	✓	✓
3.	Pyrimethamine + Sulfadoxine	✓	✓	✓
4.	Amoxicillin + Clavulanate Potassium	X	X	✓
5.	Ethinylestradiol + Levonorgesterol	✓	X	✓
6.	Ethambutol + Isoniazid + Rifampicin	X	X	✓
7.	Ethambutol + Isoniazid + Pyrazinamide + Rifampicin	X	X	✓
8.	Lamivudine + Nevirapine + Stavudine	X	X	✓
9.	Isoniazid + Rifampicin	X	✓	✓
10.	Ferrous sulphate + Folic acid	✓	✓	✓
11.	Aluminium hydroxide + Magnesium Trisilicate	✓	✓	X
	Total	6 (7%)	5 (6%)	9 (11%)

Note: '✓' denotes the presence, 'X' denotes absence