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JEMP

JOURNAL OF EUROMED PHARMACY

PHARMACEUTICAL CARE INTERVENTIONS AT THE REHABILITATION HOSPITAL KARIN GRECH

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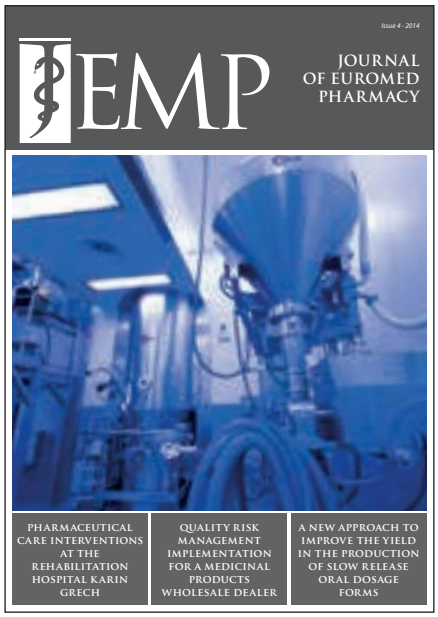

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and
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Editorial Mission:
JEMP publishes original research manuscripts, subject reviews and other contributions related to all aspects of research within the field of pharmacy. JEMP is dedicated to improve the dissemination and interpretation of results of scientific investigation and evaluation of pharmacy processes, pharmaceutical services and interventions and economic outcomes of pharmacy services.

PHARMACEUTICAL TECHNOLOGY

The production of good quality medication which is safe and effective for the patient, requires the use of state-of-the-art equipment. The choice of types of equipment used to achieve this purpose is vast, ranging from blenders, used to ensure that the mixture containing the excipients and the active pharmaceutical ingredient is homogenous, to tabletting machines and coaters. There are two types of coaters, a fluidised bed coater or a coating pan. The application of a coating may serve for two main purposes, to increase aesthetic appeal of a tablet which can be done by applying a colour to mask an unattractive colour or to confer a function for example to give slow release properties or control the site where the drug is released.

All students reading for a pharmacy degree or for a Bachelor of Science (Hons) in Pharmaceutical Technology degree are exposed to the daily activities taking place within the pharmaceutical industry through a number of industrial visits. During the visits students have the opportunity to appreciate the different steps involved, from synthesising the active pharmaceutical ingredient to manufacturing, testing and distributing the medication. In every step of the production cycle, students can identify the specialised equipment used to achieve the intended purpose.

Participation in these visits gives the opportunity to students to bridge the practical aspects with the theoretical ones learned during lectures. The various study units followed during the Pharmaceutical Technology course, namely Pharmaceutical Process Technology, Active Pharmaceutical Ingredients Manufacture, Production and Operations Management and Pharmaceutical Quality Control, equip the students with the knowledge required to carry out the daily activities within the pharmaceutical industry.

This year marks the first time during which the first intake of Pharmaceutical Technology students will graduate after following a course of three years. This course in Pharmaceutical Technology aims to target the needs of society in the health sector and pharmaceutical industry. The views and perspectives of stakeholders on the course have been extremely positive from all aspects but especially from the opportunity to host the Pharmaceutical Technology students during their academic placements.

CONTENTS

EDITORIAL

The Minister of Education, Evarist Bartolo has stated that "there is general consensus that high quality education is essential not only for an individual's success but also for the social and national socio-economic development of Malta. This puts further pressure on the education system to deliver as well as to adapt to the ever-changing landscapes of global economies."

This is exactly what the Department of Pharmacy of the University of Malta is continuously working upon. The Research Component of the Master of Science programme is an example of how tertiary education programmes offered to our pharmacy post-graduate students has succeeded not only to achieve a high quality education but also to intermingle the academic virtues with the needs of society encompassing the ever evolving state of pharmacy practice.

A casual look at the Table of Contents of this journal indicates how the topics tackled by the authors dealing with clinical pharmacy interventions, industrial pharmacy process improvements and pharmaceutical regulatory affairs point towards the correlation that exists between the pharmacy education system at the University of Malta and applied research to realistic contexts. The future evolvement of pharmacy processes such as pharmacist prescribing, clinical pharmacy, industrial production of specialised medicinal products and advanced pharmaceutical regulatory affairs are the topics covered in this journal and the findings are all a result of research carried out by pharmacists researchers who graduated with a Masters in Science in Pharmacy last November.

This achievement has prompted the Department of Pharmacy to think out of the box. It embarked on a new course leading to the Bachelor of Pharmaceutical Technology degree. The first group of students have reached the third and final year of the degree course and there are twelve students currently following the first year. The feedback on the course, which has a significant experiential placement component, albeit very demanding both on the academic staff and students, is very favourable. The uniqueness of this new course is that it is carefully planned to ensure that it does not only meet the stringent demand of an Honours Bachelors degree in the sciences but that it also meets the needs of society as it is adapted to the "ever changing landscapes of global economics". It is estimated that about 20 of the BSc (Hons) in Pharmaceutical Technology graduates are needed every year to meet local needs in the area. It is now up to all of us to ensure that enough guidance is provided to students to join the course and that dissemination of the outstanding success of this new course is carried out. It is also hoped that graduates from this course receive due recognition through an appropriate registration system.

The educational development in pharmacy is an example of a dynamic evolvement to meet the changing needs of society. The course leading to registration as a pharmacist has also been successfully recently re-designed. The programme consists of studies over 11 semesters where after the first 8 semesters, the degree of Bachelor with Honours in Pharmaceutical Science is awarded and after a further 3 semesters, the postgraduate degree of Master of Pharmacy is awarded. The Master of Pharmacy degree is required to register as a pharmacist.

The peak of achievements in pharmacy education is aimed to be reached this October 2014 with the introduction of a professional doctorate in pharmacy (PharmD), a first for the University of Malta. The course is planned to meet local and international needs in pharmacy taking into consideration the "ever-changing landscapes of global economies". The course duration is of 3 years and is open to pharmacists qualified to practice pharmacy. The placement and research components of the course provide the possibility of candidates to develop their skills in areas where the need exists. These areas include clinical pharmacy aspects both in the ward and the community setting leading to expansion of pharmacist roles in these areas, management of clinical trials, regulatory affairs such as dossier presentation and assessment, pharmacoeconomics and pharmacovigilance. The course will look into tomorrow's pharmacists contribution in areas dealing with gene therapy, biosimilars, personalised patient care, clinical pharmacokinetics in addition to developments in access to medicines, intravenous preparations, drug interactions and incompatibilities, point-of-care testing, patient profiling, adverse drug reactions prevention and reporting and disease registers.

The PharmD course is meant to attract a number of International and European students giving the opportunity to candidates to share knowledge and expertise in an international academic environment. The course is being offered in collaboration with the College of Pharmacy of the University of Illinois at Chicago. This collaboration enhances the envisaged international excellence of this professional doctorate (Level 8 degree) programme. Pharmacists with a drive to contribute significantly to the evolvement of pharmacy are encouraged to take up this opportunity. Opportunity is also provided for those interested to take up selected modules or to opt for parts of the course that lead to the award of a Diploma or Masters in Advanced Clinical Pharmacy.

The editorial board would like to recognise the contribution of Actavis, who are supporting this journal, through a collaborative agreement with the Department of Pharmacy.

Professor Anthony Serracino-Inglott

JOINING THE PROFESSIONAL DOCTORATE IN PHARMACY

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What is the Pharm D course?

The Pharm D programme is a new course being offered by the Department of Pharmacy of the **University of Malta** in collaboration with the College of Pharmacy at the **University of Illinois at Chicago** in Chicago, USA. This course was developed to provide for the rapidly growing niche area in pharmacy related to a professional doctorate. It is a means to develop professionals with a research-oriented approach and with skills in advanced clinical pharmacy practice.

Pharmacists who would like to take up the area of clinical pharmacy as their specialisation will be able to develop the skills and attributes of undertaking research in the field while reading for a level 8 doctorate-level degree.

This course will prepare graduates who are able to deliver a significant contribution to pharmacy practice and policies in clinical pharmacy and applied areas.

Course Details

- The programme is delivered using a blended learning model that includes lectures, distance-learning and practice-based learning
- Integrate learning experience with assessment and contextualization in professional practice
- Course includes a number of taught modules as well as clinical experience and research modules
- Based over three years of study covering a total of 9 semesters
- Successful completion of 90 ECTS will entitle students to a Masters in Advanced Clinical Pharmacy if they opt not to proceed with the course

Skills Developed

- Cooperate and collaborate with healthcare professionals and patients to provide individualised treatment and support patient care
- Manage medication knowledge, mitigate errors and support decision-making based on evidence-based sources, including information technology
- Efficiently collect, analyse and apply required literature sources for the appropriate clinical management of patients
- Evaluate, analyse and synthesise information and knowledge available to undertake and propose rational decisions
- Identify opportunities for improvement of a medication-use system
- Collect and critically assess clinically relevant data to facilitate monitoring and management of drug therapy plans
- Contribute significantly to development of practice research

Career Prospects

The programme will empower pharmacists practising in the professional areas to take up leadership roles that will drive policies, developments in clinical practice and service provision which draw on a scientific and evidence base.

Contacts

UNIVERSITY OF MALTA
L-Università ta' Malta

Professor Lilian M. Azzopardi
Department of Pharmacy
University of Malta
lilian.m.azzopardi@um.edu.mt
Tel: (356) 21 344 971

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Professor Alan Lau
College of Pharmacy
University of Illinois at Chicago
alanlau@uic.edu

PHARMACEUTICAL CARE INTERVENTIONS AT THE REHABILITATION HOSPITAL KARIN GRECH

Khaled Abdelmaula, Lilian M. Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida.

Corresponding author: Khaled Abdelmaula
E-mail: pharmadr@yahoo.com

ABSTRACT

OBJECTIVE To record the type and number of interventions made by pharmacists, to document intervention outcome and to record physicians' acceptance of pharmacists' recommendations.

METHOD A retrospective study was undertaken to collect data about patients who received recommendations by pharmacists during their hospital stay at the Rehabilitation Hospital Karin Grech (RHKG). This study was carried out over a 12-week period. Five hundred patient profiles were selected randomly from a sample of 1500 profiles. Analysis of data was carried out using Microsoft Office Excel® 2010 and SPSS® Version 20.

KEY FINDINGS Out of 500 patients, 323 (64.6%) received pharmacist recommendations. Out of these patients, 27% were male (n=87) and 73% were female (n=236), and the average age was 80.3 years. Patients' mean number of long term medications was 8.59 with a median of 8. 'Orthopaedic' conditions were the most common reason for admission, representing almost one third of all reasons for admission (n=96, 29.7%), followed by 'cardiac' conditions (n=62, 19.1%). A total of 1069 valid recommendations were identified in this study. 'Need for additional drug' was the most common type of pharmacists' recommendation. Of the 1069 recommendations, 77% were accepted by physicians (n=823), 19.2% were not accepted (n=212) and 3.5% could not be evaluated for acceptance (n=34). Recommendations classified as 'need for monitoring' had the highest percentage of acceptance (89.9%).

CONCLUSION The goal of this study was to evaluate the recommendations made by pharmacists in the care of elderly patients. Pharmacists made many recommendations that affect the care of hospitalised patients with the majority of recommendations being accepted by physicians. The study confirms the need for the currently offered clinical pharmacy service to improve patient care.

KEYWORDS pharmacists' recommendations, intervention, pharmaceutical care, elderly patients

INTRODUCTION

According to the definition by Hepler and Strand, pharmaceutical care is the responsible delivery of pharmacotherapy with a definite outcome aimed at improving the quality of life of the patient.[1] Pharmaceutical care is based on a relationship between the patient and the healthcare team, who together collaborate to optimise medication therapy and promote patient health.

The pharmaceutical care plan is a tool used by the pharmacist to provide pharmaceutical care. The plan has two main criteria; to ensure the patient is provided with pharmaceutical care as needed and to document actions the pharmacist has taken to improve delivery of pharmaceutical care.[2] The setting of this study was a rehabilitation hospital, RHKG, which is a 280-bed hospital that focuses on the treatment and rehabilitation of acute and chronic conditions in patients who are sixteen years of age and older.

The aims of the study were to evaluate and quantify the impact of pharmaceutical care interventions made by pharmacists at RHKG. The objectives were to record the type and number of interventions made by pharmacists, document the intervention outcomes and to record the physicians' acceptance of pharmacists' recommendations.

METHOD

Approval from the RHKG Research Committee and University Research Ethics Committee was granted. A comprehensive literature review relating to pharmaceutical care issues, interventions, recommendations and clinical pharmacy services was undertaken.

A pharmaceutical recommendation was identified from the patient profile documentation as any documented intervention made by pharmacists with the intent of improving patient therapy or quality of life.

A patient profile documentation form has already been standardised by the pharmacists working at RHKG. The patient profile includes: Patient demographics, reason for admission, admission date, medical and drug histories and type of recommendations.[3] There are thirteen types of recommendations that have been used in this study as outlined in Table 1.

Five hundred patient profiles were randomly chosen from a sample of 1500 profiles and a pharmaceutical recommendation was identified from the patient profile documentation as any documented intervention made by pharmacists with the intent of improving patient therapy or quality of life, including recommendations that do not directly involve patient's drug management, such as drug monitoring.[4]

RESULTS

Out of the 500 patient profiles reviewed in the study, there were 323 (64.6%) patients who had a pharmaceutical recommendation. Out of these patients, 26.9% were male (n=87) and 73.1% were female (n=236). The average age was 80.3 years. Patients' mean number of long-term medications was 8.59 with a median of 8. Orthopaedic conditions were the most common reason for admission, representing almost one third of all reasons for admission (n=96). A total of 1069 valid pharmacist recommendations were obtained. Table 2 shows the distribution of pharmacists' recommendations.

Indication	• Need for an Additional Drug: Untreated indication • Unclear or Unconfirmed Indication: Need for additional diagnostic test and review • Unnecessary Treatment: No appropriate medical indication; therapeutic or pharmacological duplication; drugs used for the treatment of avoidable adverse drug reactions (ADRs)
Effectiveness	• Improper Drug Selection: Drug not indicated for condition; more effective drug available; contraindication present • Dosage Too Low (Sub-therapeutic Dose)
Safety	• Dosage Too High (Overdose) • Risk for Adverse reaction/s: Unfavourable safety profile • Risk for Drug-Drug Interaction(s) • Need for Monitoring • Need for Counselling • Need for Seamless Care
Compliance	• Inappropriate compliance
Administration	• Wrong drug, dose, formulation and/or time or no drug administered

Table 1: Pharmaceutical Care Issues Classification at RHKG

The percentage of patients receiving a recommendation in this study was 64.6% (n=323) with a mean of 2.14 recommendations per patient.

Recommendation	Example
Need for Additional Drug (n=339) 31.7 %	*Heart failure; patient needs ACE inhibitor therapy*
Need for Monitoring (n=155) 14.5%	*Monitor liver function tests every six months in patient on amiodarone*
Dosage Too High (n=119) 11.2%	*Decrease dose of bendroflumethiazide prescribed for hypertension to 2.5mg daily (from 5mg daily)*
Risk for Adverse Reaction (n=90) 8.55%	*Change perindopril in patients with persistent dry cough to valsartan*
Dosage Too Low (n=67) 6.26%	*Change dipyridamole 25mg tds to 100mg tds*
Risk for Drug-Drug Interaction (n=38) 3.60%	*Ciprofloxacin in patient with warfarin therapy*
Counseling Need (n=38) 3.60%	*Patient on inhaler treatment*
Improper Drug Selection (n=37) 3.46%	*Sedentary patients on nitrates with hypotension*
Wrong Drug, Dose, Formulation and/or Time (n=25) 2.33%	*Change IV antibiotics to oral formulation*
Seamless Care (n=14) 1.40%	*Advising nursing home to make sure that patient takes alendronic acid with plenty of water while sitting or standing, at least 30 minutes before breakfast*
Contraindication Present (n=9) 0.84%	*Change amlodipine to ACE inhibitor in hypertensive patient with diabetes*
Inappropriate Compliance (n=6) 0.56%	*Patient is using wrong inhaler technique, in which case the pharmacist would explain how to use the device*
Unclear/Unconfirmed Indication (n=5) 0.46%	*Patient on omeprazole with no bleeding risk*

Table 2: Distribution of the Pharmacist Recommendation by Category Type

Pharmacists make many recommendations that affect the care of hospitalised patients, the most frequent of which were: 'Need for additional drug', 'Unnecessary Treatment', and 'Dosage too high'.

On follow up of the 1069 recommendations, 77% were accepted by physicians (n=823), 19.2% were not accepted (n=212) and 3.5% (n=34) could not be evaluated for acceptance. All recommendation categories had a higher likelihood of being accepted rather than rejected. Recommendations classified as 'need for monitoring' had the highest percentage of acceptance with 89.9%. The highest percentage of rejected recommendations was 'need for additional drug' with 27.7%.

DISCUSSION

This study evaluated the impact of the clinical pharmacy services at RHKG, by recording the type and number of pharmacist recommendations and the outcome. The percentage of patients receiving a recommendation in this study was 64.6% (n=323) with a mean of 2.14 recommendations per patient. This observation is in agreement with the earlier study by Vella[4] in 2009, carried out in the same setting.

By reviewing the pharmacists' recommendations documented, 'need for additional drug' was the most common intervention made by pharmacists in RHKG (31%), followed by 'need for monitoring' (14.5%) and 'dosage too high' (11.2%). These results indicate that the pharmacists' role in hospitals is very important in patients' therapy and to provide advice to other healthcare professionals on the effects of medications. Sellors et al. in 2003 reported that in a study carried out in a primary care setting, the addition of a medication is the most common recommendation.[5]

Physicians accepted advice on most of the recommendations proposed by pharmacists (77%). Possible reasons for not accepting the rejected recommendations are that a patient's medication would have been commenced by a specialist and the physician would be reluctant to override the initial prescribing decision, or the physician might not consider the recommendation a priority. In a study by Ling in 2005, to evaluate clinical pharmacist involvement in the emergency department, the pharmacist's advice was accepted in 89% of cases.[6]

Future studies could directly evaluate clinical improvement and medication effects including medication adherence or patient-relevant outcomes such as clinical status or quality of life measures arising from pharmacists' recommendations. Future work could also address cost-effectiveness of pharmacists' recommendations through assessment of specific costs associated with each recommendation. This will enable the pharmacy department to demonstrate the importance of pharmaceutical care and the financial savings pharmacists can achieve. Schumock et al in 2003 state that "For every $1 invested in clinical pharmacy services, $4 in benefit is expected."[7]

CONCLUSION

The goal of this study was to record and evaluate the recommendations made by pharmacists in RHKG. The study provided several important insights. Pharmacists make many recommendations that affect the care of hospitalised patients, the most frequent of which were: 'Need for additional drug', 'Unnecessary Treatment', and 'Dosage too high'. Physicians accepted advice on the vast majority of recommendations proposed by pharmacists.

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MANAGEMENT OF URINARY TRACT INFECTIONS IN ELDERLY AT THE REHABILITATION HOSPITAL KARIN GRECH

Asma Omar Ali, Lilian M. Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida.

Corresponding author: Asma Omar Ali
E-mail: asmaomer@ymail.com

ABSTRACT

OBJECTIVE To assess the percentage of patients suffering from urinary tract infections (UTIs) who were treated at the Rehabilitation Hospital Karin Grech (RHKG) and to evaluate treatment choices used to manage UTIs at the same hospital during a one-year period.

METHOD A retrospective and current study were carried out to collect information about patients who were diagnosed with UTIs namely age, gender, medical history, medications and presence of a catheter. This information was obtained from patient profiles in each of a total of 9 wards in the hospital. Analysis of data was carried out using Microsoft office Excel® 2010 and SPSS® version 20.

KEY FINDINGS Out of 165 UTI patients, 67% were female (n=111) and 33% were male (n=54). Thirty-seven percent of the patients were diabetic. Ninety patients had a catheter prior to the period of infection and an association between catheterisation and type and number of UTI pathogens was reported. Presence of a catheter increased the chance of being affected by two or three different types of UTI pathogens which are more resistant than pathogens which were contracted by non-catheterised UTI patients in one episode. The majority of UTI cases at RHKG were treated with nitrofurantoin (41.8%), the first line agent as mentioned in hospital guidelines, followed by ciprofloxacin and co-amoxiclav at 27.3% and 20.0% respectively. Out of the 41.8% of patients who were treated with nitrofurantoin, 30.4% had an estimated glomerular filtration rate (eGFR) and/or urinary pH unsuitable for nitrofurantoin use.

CONCLUSION A prevalence of UTIs in hospitalised patients at RHKG of 11% was identified. Catheterisation increased risk of UTI and presented with a higher number of different pathogens. Nitrofurantoin was the main antibacterial used in the management of UTIs.

KEYWORDS urinary tract infections in adults, diabetes, catheterisation, antibacterials

INTRODUCTION

Urinary tract infections (UTIs) are the most common nosocomial infections[1] and reach up to 40% of the total hospital-acquired infections.[2] Worldwide, around 150 million persons are diagnosed with UTIs per annum, costing the global economy approximately 6 billion US dollars.[1] UTIs are exacerbated in elderly people in communities and long term health care centres[3] due to decreased functional capacity and increased use of medications.[4]

The aims of the study were to identify the occurrence of UTIs in patients at RHKG, evaluate treatment choices adopted in the management of UTIs and to identify correlation factors with diabetes and catheterisation.

METHOD

The study was approved by the University Research Ethics Committee. An extensive literature review on the management of urinary tract infections was undertaken. A retrospective and current study of inpatients who were diagnosed with UTIs was carried out in each of a total of 9 wards in the hospital during the one- year study period. In the first retrospective stage, the information was obtained from patient profiles which were included in the archive of the pharmacy department. In the second stage, patient information was obtained whenever new cases of UTIs were recorded at RHKG. The study design was based on classifying patients into groups according to type and number of microorganisms, antibacterial therapy which is used to treat UTI patients, co-morbidities (diabetes mellitus) and whether the patient is catheterised or not.

The research setting was the RHKG, a 280-bed hospital targeted for the treatment and rehabilitation of patients who are sixteen years of age and older, with the majority of patients being over sixty years. Patients are referred from the acute hospital or their home.

Out of 96 patients who were treated with second line antibiotics, the reasons behind prescribing second line treatment were renal impairment, urinary pH and sensitivity.

Analysis of data was carried out using Microsoft office Excel® 2010 and SPSS® version 20. The chi-squared test of association was applied to study associations between age and gender, catheterised and non-catheterised patients, number and types of pathogens and recurrence of UTIs, diabetes and pathogen types.

RESULTS

During the study period, there were a total of 1564 admissions of which 61.76% were female patients. The mean age of patients and length of stay were 79.7 years and 46.7 days respectively. Eleven percent of the patients (n=165) suffered from UTIs during their hospitalisation period. Most of the patients complained of urgency, frequency, burning sensation during urination, abdominal or loin pain, discolouration of urine and fever.

Out of the 165 UTI patients, 67% were female (n=111) and 33% were male (n=54) (Figure 1). The number of females suffering from UTIs was double that of males. The highest proportion of male patients suffering from a UTI fell in the 71-80 age range, while the majority of female patients with a UTI fell in the 81-90 age range.

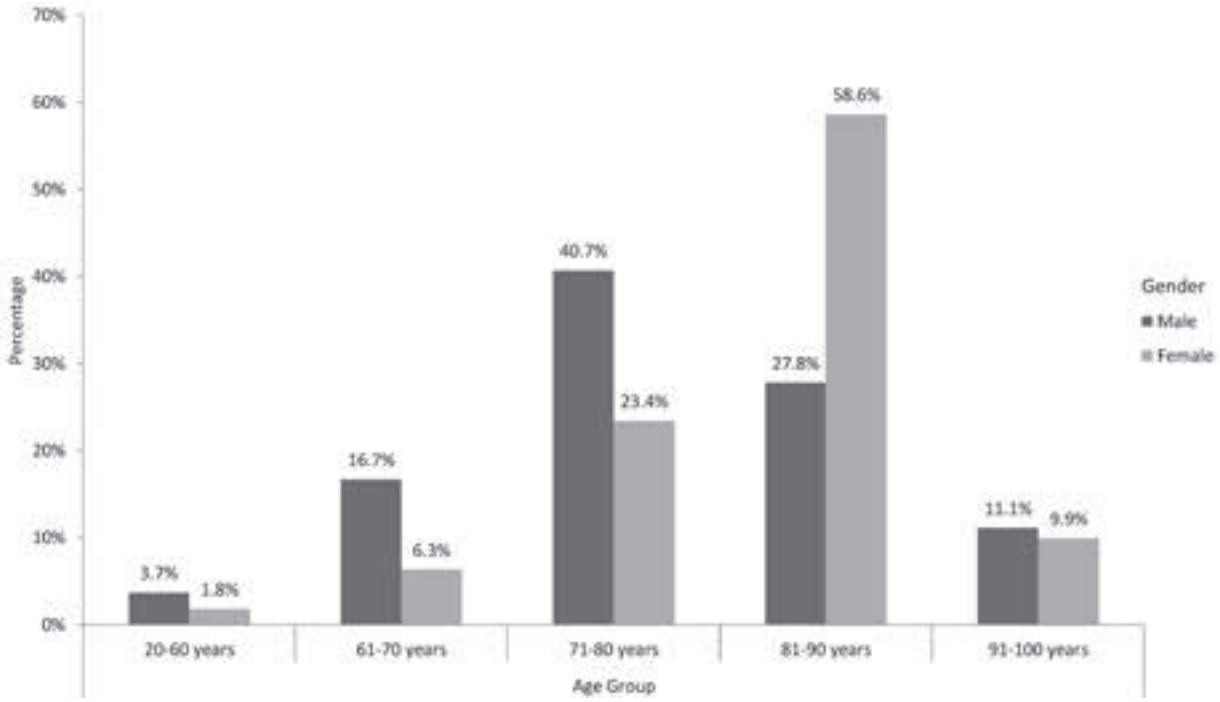

Figure 1: Gender and Age Groups (N=165)

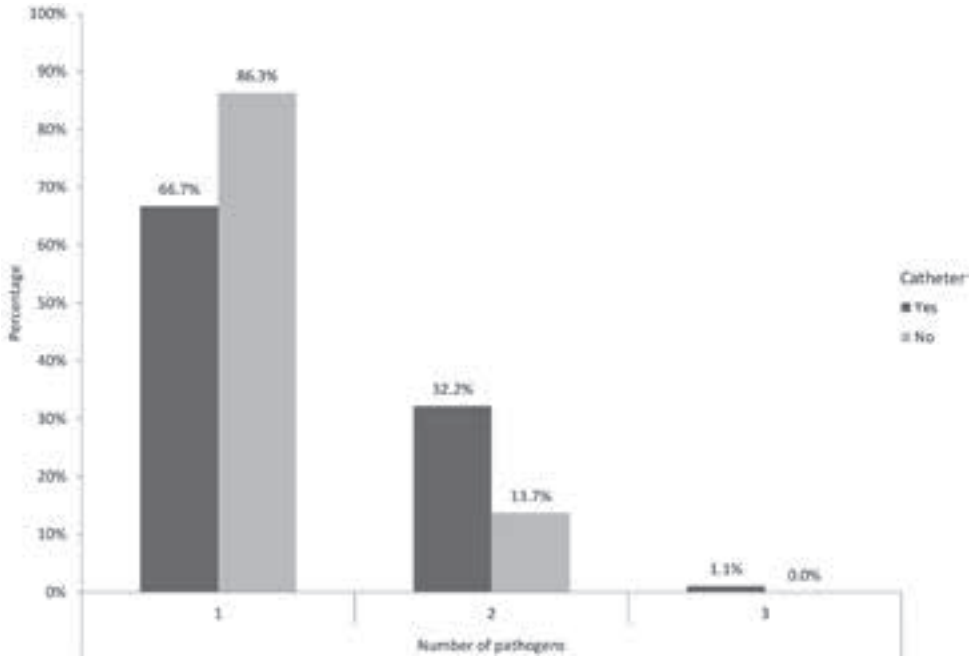

Figure 2: Catheterisation and Number of UTI Pathogens (N=165)

Out of the 165 patients, 54.5% (n=90) had a catheter prior to the infection period. Patients with a catheter are more likely to have more types of pathogens such as *Serratia marcescens* and *Providencia stuarti* than the pathogens that appear in non-catheterised patients. These new pathogens are also more resistant than the pathogens in non-catheterised patients, for instance, *E. coli* ESBL and *Staphylococcus aureus* MRSA. Catheterised patients have almost double the number of pathogens than non-catheterised patients ($\chi^2 = 40.597$, v = 19, p = 0.003).

Figure 2 indicates the number of pathogens responsible for UTIs per patient in terms of presence or absence of a catheter. Patients without a catheter are more likely to have just one type of pathogen when compared to catheterised patients (86.3% as opposed to 66.7%). Catheterised patients have a higher chance of having two or three types of pathogens at the same time when compared to patients having no catheter (33.3% as opposed to 13.7%). The presence of a catheter leads to an increase in the number of pathogens in one episode of UTI ($\chi^2 = 8.574$, v = 2, p = 0.014).

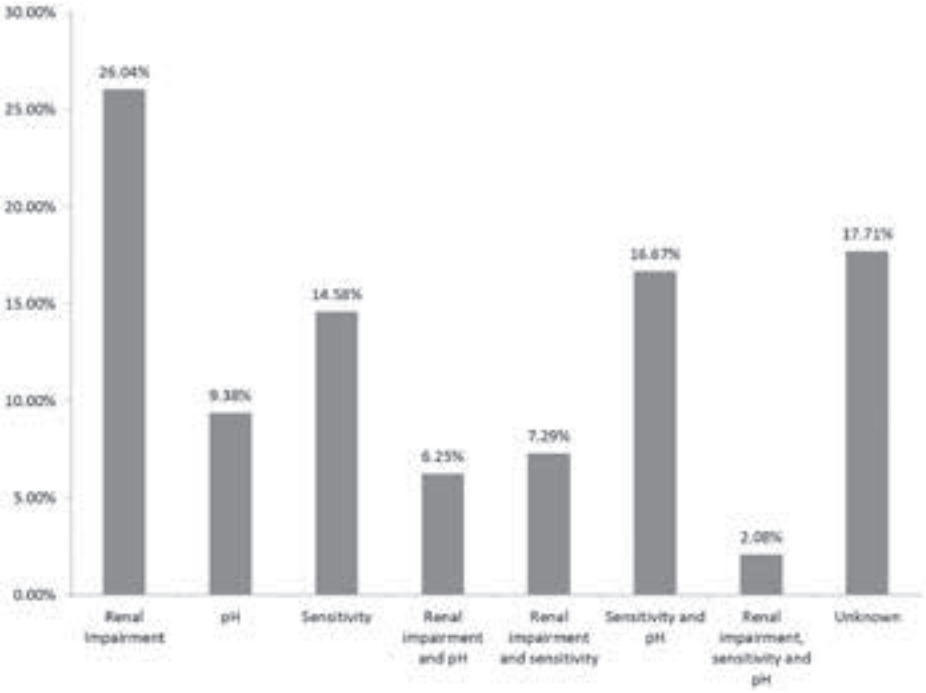

Figure 3: Reasons of Prescribing the Second Line Antibiotics (n=96)

The majority of UTI cases were treated with nitrofurantoin, which amounted to 41.8%. This was followed by ciprofloxacin and co-amoxiclav at 27.3% and 20.0% respectively. Out of 96 patients who were treated with second line antibiotics, the reasons behind prescribing second line treatment (Figure 3) were renal impairment, urinary pH and sensitivity. These reasons were either separate or were present simultaneously.

DISCUSSION

In this study females presented a higher prevalence of UTIs, however there is a higher proportion of female patients in the hospital. This finding is in agreement with a study carried out by Raz et al. in 2000.[4] More than one third of UTI patients at RHKG had diabetes mellitus (36.97%, n=61) with 25 were males and 36 females. No association between gender and diabetes was found in this group (p-value=0.083) and there was no association between diabetes and type of UTI (p-value=0.344). In this study more than half (54.5%) of UTI patients at RHKG had a catheter before they contracted UTIs and over two thirds of these, (70.37%) were male patients suffering from prostate problems.

Out of a total of 19 pathogens, *E. coli* was found to be the main aetiological factor for UTIs (46.1%). This was followed by *Enterococcus faecalis* (13.9%), *Proteus mirabilis* (11.5%) and *Pseudomonas aeruginosa* (9.7%). In terms of pathogen types, catheterised patients are more likely to have resistant pathogens when compared to non-catheterised patients (p-value =0.003). Catheterised patients have a higher chance of having two or three types of pathogens in one episode compared to non-catheterised patients (p-value=0.014). This is confirmed by a number of studies including a five year study in a hospital in the United Kingdom where it was reported that polymicrobial presentation in catheterised patients has increased and a change in antimicrobial resistance has been noted.[5]

CONCLUSION

The goal of this study was to assess the percentage of UTI patients who were treated at RHKG and evaluate treatment choices used to manage UTI patients in this hospital. The study provided several important insights into the prevalent pathogens causing UTIs and use of antibacterial agents. The use of nitrofurantoin is adopted as first line management in accordance with UTI hospital guidelines. However, considerations where nitrofurantoin should be avoided may need to be emphasised.

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PHARMACISTS PRESCRIBING OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Maria Scerri, Lilian M.Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida.

Corresponding author: Maria Scerri
E-mail: maria20scerri@gmail.com

ABSTRACT

OBJECTIVE To develop, implement and validate a framework and protocol directed to pharmacists regarding prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and to propose a documentation system to be used when prescribing NSAIDs.

METHOD A module highlighting the information on NSAID use and on pharmacists prescribing of NSAIDs was developed to be used as a tool for development of pharmacists' knowledge to participate in the framework of pharmacist prescribing of NSAIDs. A protocol to be used when prescribing NSAIDs was developed. The developed protocol is concise and includes all relevant data. Evaluation of the proposed module and protocol was carried out by an expert panel consisting of 14 professionals. The readability of the module was assessed. A documentation system was set up using Microsoft Excel® 2007.

KEY FINDINGS A module named 'Supplementary Prescribing for Pharmacists' was developed as a Power point Presentation using Microsoft PowerPoint® 2007. The final version of the module scored 55 in the Flesch Reading Ease formula. The expert panel rated the overall presentation as very good. The module was considered a good tool of information for its intended purpose. Eleven healthcare professionals found the module very helpful and 7 found it very practical for its intended use. A protocol named: 'Protocol for Prescribing NSAIDs' was developed. Twelve health care professionals found the protocol easy to use while 5 of the participants thought it was time consuming.

CONCLUSION The module and protocol were very well accepted by the expert panel. Up till now there was a lack of protocols regarding NSAID use in Malta and that some potential side effects pertaining to this class of drugs were not always taken into consideration while dispensing. This study is now proposing a module to establish a safe and standard practice for recommendation of use of NSAIDs.

KEY WORDS Pharmacists prescribing, NSAIDs, Protocol

INTRODUCTION

Pharmacists are healthcare professionals, who are experts in safe and effective medication use. Pharmacists prescribing may lead to the full use of this expertise and thus benefiting from the full potential of the pharmacy profession. With the introduction of pharmacists prescribing rights, health care delivery would improve and time and cost to deliver patient care, would be reduced.

There are two types of pharmacists prescribing, dependent and independent prescribing. In dependent prescribing, the physician and the pharmacist have equal responsibilities towards patient's health. The physician diagnoses and makes treatment decisions whilst the pharmacist may select, monitor, modify or discontinue drug therapy.[1,2]

In independent prescribing, the pharmacist prescriber takes responsibility for the clinical assessment of the patient by establishing a diagnosis, deciding the clinical management required and taking responsibility for appropriately prescribing where necessary.[1,2]

NSAIDs are known to cause gastrointestinal events which may cause complications such as gastro-intestinal ulceration and bleeding.[3-9] They are also known to cause cardiovascular events such as increasing the risk of a myocardial infarction in susceptible patients.[6,10-13] Other adverse effects of NSAIDs include renal impairment which leads to an increase in blood pressure if the patient is already hypertensive[8,9,15] and induction of bronchospasms especially if the patient already suffers from asthma.[4,16,17] All these side effects and drug-drug interactions warrant pharmacists within an independent or dependent prescribing scenario to ensure patient safety.

The aims of the study were to develop and validate a framework and a protocol directed to pharmacists regarding prescription of NSAIDs and to propose a documentation system to be used when prescribing NSAIDs.

METHODOLOGY

A module highlighting the information on NSAID use and pharmacists prescribing of NSAIDs was developed to be used as a tool for continuous development of pharmacists' knowledge. This was done after thorough research regarding this class of drugs.

A protocol to be used as an aid for the safe prescribing of NSAIDs was then drafted using Microsoft Word®2007.

This module could be used in conjunction with a prescribing module to support pharmacists develop pharmacist prescribing for NSAIDs.

After the module and protocol were ready, a documentation system was drafted with the help of a physician to ensure that all necessary data was included whilst keeping record of the prescribing activity.

Health care professionals were asked to give feedback regarding the information on these tools using, a questionnaire which was developed and disseminated as a hard copy and an online version. The Chi square test were used when 2 categorical variables needed to be analysed.

RESULTS

Out of the 20 health care professionals contacted, 14 answered the questionnaire, with 7 being physicians and/or consultants and the other 7 being pharmacists. When comparing level of education with the profession it was observed that most pharmacists did not continue to post tertiary education as opposed to physicians (χ^2 (1) = 7.778, p=0.005).

The module proposed was considered to be professional by 13 out of the 14 health care professionals in the expert panel. Its presentation and writing style were well accepted by the panel which rated the module as very good and/or excellent. The language, words and technical terms used were all considered understandable by 93%, 100% and 86% of the expert panel respectively (χ^2 (2) = 2.154, p=0.341). Seventy one per cent (n=10) of the expert panel rated the way the module was written as very good. The Flesch Reading ease score of the module was found to be 55. The module was found to be very helpful and very practical for its intended use by 9 physicians and 8 pharmacists (χ^2 (1) = 0.150, p=0.699).

Although the proposed protocol was seen as very easy to use by 93% (n=13) and the incorporated flow charts were rated as very clear and clear by 8 and 6 health care professionals respectively, it was found to be time consuming by 43% (n=6).

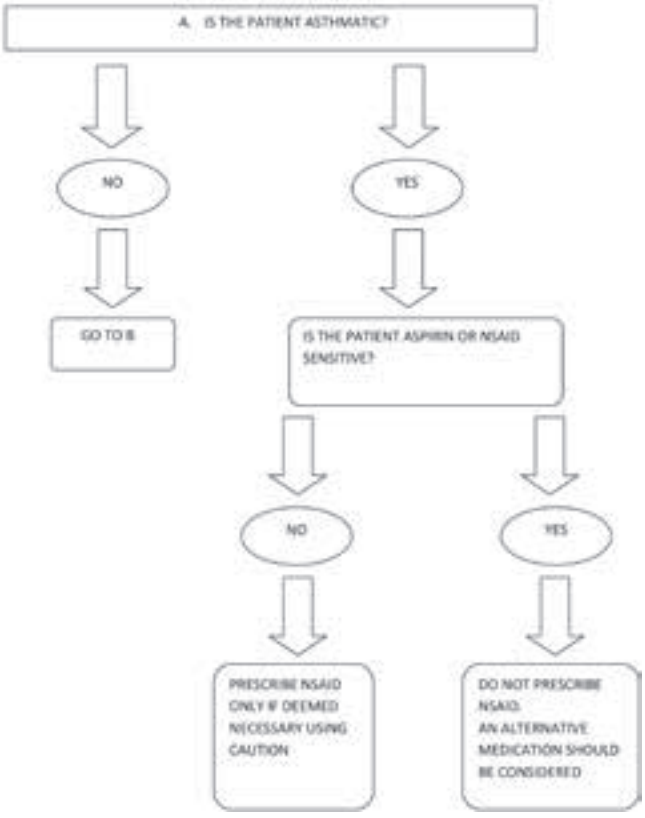

Figure 1: Part of Proposed Protocol regarding NSAIDs

DISCUSSION

When comparing the level of education with profession, it was observed that since the p-value obtained (0.005) is less the 0.05 level of significance, physicians tend to further their studies to a post tertiary level significantly more than pharmacists.

For the proposed module, a Flesch Reading ease score between 10 till 40 was aimed for, since it is targeted for professional people who have graduated with a University degree in pharmacy. The final version of the module scored 55 in the Flesch Reading Ease score which is deemed satisfactory for this type of audience composed of graduated professionals.

There was no statistical difference (p=0.341) between how health care professionals rate the language, words and use of technical terms, which were found to be very understandable. The module was found to be very helpful and practical for its intended use. There was no statistically significant difference between helpfulness and practicality of the module (p=0.699).

The proposed protocol was found to be time consuming by almost half of the expert panel, whilst almost all experts found the protocol to be easy to use and rated the steps as clear. One limitation of the study was that a small sample size was used to evaluate the module and protocol. It is recommended that the evaluation is implemented on a larger scale. The module included all information regarding safe use of NSAIDs but no information regarding prescribing skills. These skills are taught to physicians and are gained through experience. Information regarding such skills could be inserted in the module.

CONCLUSION

The module regarding NSAIDs and the protocol regarding the use of these drugs suggested in this study are well accepted by both pharmacists and physicians. This module could be used in conjunction with a prescribing module to support pharmacists develop pharmacist prescribing for NSAIDs.

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QUALITY RISK MANAGEMENT IMPLEMENTATION FOR A MEDICINAL PRODUCTS WHOLESALE DEALER

Adrian Busuttil, Anthony Serracino-Inglott
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida

Corresponding Author: Adrian Busuttil
E-mail: busuttila@gmail.com

ABSTRACT

OBJECTIVES The aims of this study were to compile a model of a Quality Management System (QMS) for distribution of medicines, identify the risks in distribution to the quality of medicinal products from a Maltese wholesale dealer's perspective and evaluate these risks using Quality Risk Management (QRM) methodology. The ultimate objective was to indicate whether risks are being well managed and to propose appropriate corrective and preventive actions (CAPA).

METHOD A set of model Standard Operating Procedures (SOPs) which describe the current wholesale dealer's operations was compiled. These SOPs were written in simple English to facilitate comprehensiveness by the employees. The various steps in the distribution of medicinal products by a wholesaler and the risks in each step were identified and a flowchart was compiled. A QRM assessment was carried out, taking into consideration current risk management activities described in SOPs. No further action was recommended for risks which were deemed as acceptable, however appropriate CAPA was recommended for risks deemed as being unacceptable.

KEY FINDINGS Out of 70 identified risks during QRM evaluation, 65 risks were deemed acceptable, while 5 were deemed not acceptable. Areas exhibiting unacceptable risks were 'Returns of medicinal products' (1 risk) and 'Temperature monitoring and control during shipment from supplier' (4 risks).

CONCLUSION CAPA was proposed to change the profile of unacceptable risks. A model QRM SOP was compiled to be used by Maltese wholesale dealers in setting up a QRM system and to help in fulfilling regulatory obligations.

KEYWORDS Quality Management System, Quality Risk Management, Standard Operating Procedure, Corrective and preventive action, Medicinal products, Wholesale distribution

INTRODUCTION

In an effort to modernise the regulation of pharmaceutical technology and quality through international collaboration via International Conference on Harmonisation (ICH), the EU has adopted and implemented guidelines to the use of Quality Risk Management (QRM) in pharmaceutical manufacturing. These guidelines available in ICHQ9[1] have been adopted in Annex 20[2] of the Eudralex Volume 4 Good Manufacturing (GMP) Guidelines. QRM methodology has been successfully implemented in pharmaceutical manufacturing.

The need for updated Good Distribution Practice (GDP) guidelines was felt since the GDP guidelines in place have been published in 1994.[3] Following consultation with stakeholders, the European Commission published revised GDP guidelines on March 7, 2013.[4] These new guidelines direct medicinal product wholesale dealers (MPWD) to start implementing a QRM system as per QRM methodology already used in the pharmaceutical manufacturing industry to improve risk management relating to the quality of medicinal products in the legal supply chain.

This study aimed to compile a model Quality Management System (QMS) for an established MPWD, to identify and assess risks and ultimately propose appropriate Corrective and Preventive Actions (CAPA) for unacceptable risks in the distribution chain. This project also aimed to compile a model SOP to be used for QRM application by a MPWD.

METHOD

DESIGN OF MODEL QMS

The design of a model QMS for MPWD XYZ Ltd was undertaken with the scope of describing the current procedures required to ensure that distribution of medicinal products is in line with current European and Maltese legislation and current GDP guidelines.

SOP Number	Version	Name of SOP
01	01	SOP Policies and Procedures
02	01	Storage Procedures
03	01	Sale and Supply Procedures
04	01	Returns and Complaints Procedures
05	01	Recalls Procedure
06	01	Internal Audits Procedure
07	01	Verification of Supplier and Customer Status
08	01	Training
09	01	Purchase and Receipt Procedures
10	01	RP Responsibilities
11	01	Change Control and Process Deviation Procedures
12	01	Cold Chain Integrity Procedures for Verified Suppliers
13	01	Return to Supplier / Disposal of Pharmaceuticals
14	01	Stock Taking and Expired / Damaged Pharmaceuticals Handling Procedure

Table 1 – A list of compiled Model Standard Operating Procedures

These SOPs were written in simple and concise English and aim to list all the procedures carried out by a MPWD for the supply of medicinal products and to remain fully compliant with current Maltese/EU legislation and GDP guidelines. List of compiled SOPs is available in Table 1.

IDENTIFICATION OF RISKS

The main steps involved in the distribution chain from when a product is ordered from supplier until delivery to an authorised client were identified. Steps were classified as being within the MPWD's control or not. Risks within each step were identified by asking the question; 'What can go wrong?'

RISK ANALYSIS

Failure Mode Effects and Criticality Analysis (FME(C)A) was chosen as the risk assessment tool since it is recommended as a main QRM tool by ICHQ9 and Annex 20 of GMP, due to its wide use in pharmaceutical QRM[5,6] and due to its relatively ease of use.[7]

An Excel sheet was compiled with the risk description and with current risk management actions according to the QMS model. On the basis of risk and current risk management actions, a score of 1-5 was assigned for each of three factors namely severity (S), probability (P) and detectability (D). Scores were assigned as follows: the higher the severity the higher the score, the higher

the probability the higher the score and the higher the detectability the lower the score. The Risk Probability Number (RPN) was then calculated per risk by multiplying the scores of severity (S), probability (P) and detectability (D) according to the equation: RPN = S x P x D. All details were added in an Excel sheet.

RISK ACCEPTABILITY

According to the developed model, the higher the score given for severity and probability, and the lower the score given for detectability, the higher the risk. Risks were classified into two categories: 'Acceptable' risks and 'Not acceptable' risks. The lowest possible RPN mathematically is 1, while the highest possible RPN is 125. A risk with an RPN above 20 was deemed as not acceptable to ascertain a higher degree of safety.

RESULTS

In total, 16 main steps were identified and a flowchart was compiled (Figure 1) illustrating the processes involved in the flow of medicinal products at a MPWD from supplier procurement to final client delivery.

Figure 1: The various steps involved in the Distribution of Pharmaceuticals

The two areas which exhibited 'Non-acceptable' risks were 'Temperature conditions during transit' and 'Return of Pharmaceuticals'.

Seventy risks were identified and added to the flowchart in Figure 1. Using FME(C)A methodology evaluation, 65 risks were classified as 'Acceptable' (RPN ≤ 20) and 5 risks were classified as 'Not Acceptable' (RPN>20). From the 'Not-Acceptable' risks (n=5), 4 were related to temperature excursions when pharmaceuticals are transported by supplier without temperature data-logger and 1 risk is related to acceptance of returns from clients without temperature records present.

CAPA was proposed for all unacceptable risks (Table 2).

QUALITY RISK MANAGEMENT SOP

A model wholesale QRM SOP was compiled to facilitate re-evaluation of the QMS using QRM methodology by the MPWD.

DISCUSSION

MODEL STANDARD OPERATING PROCEDURES

The model SOPs drafted are based on actual SOPs in use by Maltese wholesale dealers which in turn are based on GDP guidelines. The scope of these procedures is to enable the MPWD to have as much control as possible on all operations which take place and which can impact the quality of medicinal products. Some of the procedures compiled in this study, which are still very essential for the proper functioning of a MPWD go beyond strict GDP requirements, for example pharmaceutical waste disposal.

QRM EXERCISE

The results produced by the FME(C)A evaluation showed that the vast majority of risk factors identified were being appropriately managed with current risk management actions and the latent risk is acceptable (RPN = or < 20). Since the model SOPs and operations are modelled around real wholesale dealer's operations rather than being just theoretical, this might explain why the majority of RPNs scored 20 or below. The two areas which exhibited 'Non-acceptable' risks were 'Temperature conditions during transit' and 'Return of Pharmaceuticals'. These two areas have also been identified as being problematic by the European Commission and the new GDP Guidelines aim to regulate these areas more thoroughly.

Risk Description	RPN Score	Risk Acceptability	Proposed risk minimisation and / or risk management CAPA actions
Temperature excursion during transit for room temperature pharmaceuticals (store below 25 °C) **without** data logger in place during winter	30	Not Acceptable	It is recommended that supplier includes a data logger with shipment. This will highly increase detectability and this risk can be managed as per same risk **with** data logger.
Temperature excursion during transit for room temperature pharmaceuticals (store below 25 °C) **without** data logger in place during summer	60	Not Acceptable	
Temperature excursion during transit for cold-chain pharmaceuticals (store at 2-8 °C) **without** data logger in place during summer	75	Not Acceptable	
Temperature excursion during transit for cold-chain pharmaceuticals (store at 2-8 °C) **without** data logger in place during winter	60	Not Acceptable	
Unexpired pharmaceuticals accepted into good stock that were kept in unacceptable temperature conditions at client	48	Not Acceptable	It is recommended that unless temperature records can be easily accessible and verifiable, returns of all pharmaceuticals are **not** accepted.

Table 2: Description of 'Not Acceptable Risks' and Proposed CAPA

This study shows how theoretical guidelines and recommendations of risk management as per Annex 20 and ICH Q9 can be combined with the real world scenario resulting in a comprehensive risk assessment taking into consideration the risks at each step of the distribution chain for the MPWD.

Transportation of medicinal products from the EU supplier to the Maltese wholesale dealer consists of consignments that are typically bulkier than orders supplied by the MPWD to the individual pharmacy. The shipping time to receive such a consignment is also significantly higher than the time required by the local MPWD to deliver to an authorised client such as a pharmacy. On this basis alone, the risk of temperature excursions in consignments in transit to Malta is higher. It is therefore reasonable to assume that more effort to control temperature and detect excursions should be necessary for the shipment with higher risk rather than the local deliveries. Proposed CAPA is to change commercial and technical agreement with suppliers to include temperature data loggers in consignments shipped to Maltese MPWD. The increased detectability will decrease the RPN scores to an acceptable level as per risks of temperature excursions with data loggers included.

In the current SOP model, returned medicinal products (room temperature pharmaceuticals only) are accepted provided that the pharmacist signs a form declaring appropriate storage. However, one cannot guarantee that such storage conditions where kept, since temperature records are not verified. It is suggested to amend the SOP to refrain from accepting any returns unless verified with temperature data that storage conditions at the client have been optimal.

QRM IN PRACTICE FOR A MPWD

Various examples and guidance documents were found in the literature about the use of QRM in pharmaceutical manufacturing. However, no specific information was available regarding the implementation of a QRM system for a MPWD. This study shows how theoretical guidelines and recommendations of risk management as per Annex 20 and ICH Q9 can be combined with the real world scenario resulting in a comprehensive risk assessment taking into consideration the risks at each step of the distribution chain for the MPWD. The compiled QRM SOP can be adapted by a MPWD to evaluate its QMS. Such a project needs to be constantly updated with new data to truly reflect risks or cater for new risks as required.

CONCLUSION

When implemented, the QMS and QRM systems developed in this study can help the MPWD to ensure that all distribution operations are under control and thus be in a better position to safeguard the quality of medicinal products. Through compliance with legislation and GDP guidelines, the MPWD will ensure better patient care through the availability of high quality medicinal products.

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A NEW APPROACH TO IMPROVE THE YIELD IN THE PRODUCTION OF SLOW RELEASE ORAL DOSAGE FORMS

Nicolette Sammut Bartolo, Anthony Serracino-Inglott
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida.

Corresponding author: Nicolette Sammut Bartolo
E-mail: nicolette.sammut-bartolo@um.edu.mt

ABSTRACT

OBJECTIVE The objectives of the study were to analyse a new improved method used for the production of pellets for the manufacture of solid oral dosage forms and to compare the new method with a method previously used and studied by Bartolo in 2011.

METHOD The parameters recorded during the production of slow release pellets were collected from the Batch Manufacturing and Instructions Record (BMIR). A total of eight batches were monitored and statistically analysed, using One Way Anova, to determine whether there is a statistically significant difference between the parameters of each batch. The mean surface rating of the pallets and the yield of the active pharmaceutical ingredient (API) obtained for the monitored batches, were statistically compared to those obtained in the previous study using the Independent Sample t-test. Statistical analysis was conducted using SPSS® version 20.

KEY FINDINGS Fine tuning in the control of all parameters during the manufacturing of different batches, even within established range, improves the yield of the final product.

A statistically significant improvement in the mean pellets' surface rating (*p-value* 0.004) and percentage yield of API (*p-value* 0.030) was observed in batches analysed in this study (4.75% and 94.09% respectively) when compared to batches analysed in the previous study (3.82% and 92.43% respectively) in 2011.

The batches analysed during this study achieved the required dissolution rate after the application of the second slow release coating as opposed to the batches analysed in the earlier study, which required the application of a third slow release coating.

CONCLUSION The increase in the yield of API and improvement in the surface rating of the produced pellets implies that the new approach used for the production of slow release pellets is better and improved.

KEY WORDS Slow release, yield, surface rating, solid oral dosage forms

INTRODUCTION

Coating of solid oral dosage forms is a commonly used process in the pharmaceutical industry which has been carried out for many centuries; the first records date back to the period between the ninth and eleventh century.[2-5] The coating process was initially established to apply a sugar coating on sweets and was later adapted to be used in the pharmaceutical industry. In 1954 the coating process was further adapted to develop and introduce the application of film-coatings.[6]

Tablets and pellets are mainly coated using a fluidised bed coater or a coating pan which may either be perforated or have a solid wall. When coating pellets, a solid wall coating pan must be used since pellets may clog the perforations due to their small size.

The coating pan can be divided into two zones namely the spraying and drying zone.[5-7] In the spray zone, tablets or pellets are exposed to spray pistols from which the coating solution is sprayed.[7] One or more spray pistols may be present in a system, depending on the size of the coating pan used.[8]

The sprayed solution is pumped towards the spray nozzle by means of a peristaltic pump and on exiting the nozzle, the solution combines with air sprayed at a high pressure. This action atomises the solution into droplets.[9] This type of atomiser is known as pneumatic atomiser and is mainly used for water-based coatings to aid the drying process by inducing evaporation.[6,10] This process occurs in a fraction of a second.[6] A study using the 'Discrete Element Method' to visualise the coating process demonstrated that as the coating pan rotates, the tablets or pellets present in the spray zone appear to be almost separated, for a short period of time, from those situated outside the spraying zone.[11] During the coating process only the tablets or pellets exposed to the spray jet on the surface of the bed are coated.

The aims of this study were to determine any statistically significant difference in the parameters monitored during the production of slow release oral dosage forms of batches produced using an innovative method. Any statistically significant difference between the batches produced using the new approach and the batches produced in the previous study[1] were to be determined.

METHOD

The slow release pellets were produced using a coating pan. The coated sugar spheres, which are called pellets, were then dried using an oven. After drying, the pellets were re-introduced into the coating pan where they were coated twice with a slow release coating. The last step of the process involved the filling of hard gelatine capsules with the pellets produced.

The method used for the production of the slow release pellets in this study differed from that used previously[1] where process parameters were varied occasionally during the coating process. In this study a new approach was used. Process parameters were varied throughout the production process according to the requirements of the product. For example, over wetting, which occurred as a result of high humidity, was counteracted by increasing the temperature of the air entering the coating pan and increasing the distance between the pistols and the product bed.

The application of the API-containing coating solution onto the sugar spheres and the subsequent application of the slow release coating onto the pellets were studied. The process parameters which were of interest to this study were monitored using the BMIR.

A sample was collected from each batch and examined under a microscope, to determine the pellets' surface roughness. The surface roughness was then rated accordingly from 1 to 5 (Table 1).

Rating	Pellets' Surface Description
1	Surface is densely packed with large spikes
2	Surface is densely packed with small spikes
3	Surface has some spikes
4	Surface is irregular but no spikes
5	Surface is very smooth

Table 1: The rating and corresponding description of the Pellets' Surface Roughness

A total of eight batches of slow-release pellets were monitored. The batches chosen for this study were produced using the same coating pan used in the previous study[1] to enable comparison between the different batches. This limited the number of batches which could be analysed.

Statistical analysis was undertaken using SPSS® version 20 to determine whether there was a statistically significant difference in the parameters used during the coating process of the analysed batches. This was done using One-Way Anova test.

Following statistical analysis, parameters of the analysed batches which were found to have a statistically significant difference, were further analysed using a post-hoc test to determine which batches were different.

The yield of API and the surface roughness of the pellets after the application of the API obtained in this study were compared to the previous study[1], using the Independent Sample t-test. This analysis was performed to determine whether there is a statistically significant improvement in the yield of API using the new improved method.

RESULTS

The analysed parameters included the temperature of air entering the coating pan, temperature of the product, the pistols' distance from the product bed and pump speed, that is the speed used to pump the coating solution using a peristaltic pump.

On performing statistical analysis, it was observed that the parameters analysed during the production of the batches were all statistically significantly different from each other, except for the pistols' distance during the application phase, the product temperature during the application of the first slow release coating and the pan speed during the application of the second slow release coating.

Temperature of Air Entering	Temperature of the Product
Air Inflow	Air Outflow
Pan Pressure	Pistols' Distance
Pump Speed	Pump Flow
Pan Velocity	Pre-cooling
Air Humidity	Pan Depression
Atomisation Pressure	Film Pump Flow

Table 2: Parameters found to be statistically significant different

The surface roughness of the 28 batches produced during the study conducted previously[1] was compared to the 8 batches produced in this study. The mean surface roughness of the previous batches was 3.82[1] which is lower than that obtained for the batches analysed during this study (4.75).

Study	N	Mean	Standard Deviation	Standard Error Mean
Bartolo (2011)	28	3.82	1.335	0.252
Current	8	4.75	0.463	0.164

Table 3: Comparison of Surface Roughness

The p-value obtained for the Independent sample t-test was 0.004 which is lower than the 0.050 level of significance, implying that there is a statistically significant difference in the surface rating of the batches after coating the sugar spheres with the active ingredient.

The percentage yield of API of the 30 batches analysed during the previous study[1] was compared to the batches analysed during this study.

The mean percentage yield of API for previous batches was 92.43% which is lower than that obtained for the batches analysed during this study that is 94.09%. The resultant p-value was 0.030 which is lower than the 0.050 level of significance. This implies that the null hypothesis is rejected since there was a statistically significant difference in the percentage yield of API of the analysed samples.

Study	N	Mean	Standard Deviation	Standard Error Mean
Bartolo (2011)	30	92.43	1.920	0.350
Current	8	94.08	1.468	0.519

Table 4: Comparison of Yield of API

DISCUSSION

In the innovative method developed, parameters are adjusted, while being kept within the stipulated limits, according to the requirements of the coating process.

The pellets produced with this approach did not require the application of the third slow release coating as opposed to the batches produced during the previous study.[1] They all achieved the required dissolution rate after the application of the second slow release coating despite fine tuning of the process controlled parameters.

This shows that batches may vary from one to another due to varying conditions, such as humidity. Each batch must be treated individually and the different process parameters must be finely adjusted for the production of each batch according to the varying conditions.

When comparing the pellets' surface roughness obtained during the two studies after the application of the API, a statistically significant difference was observed. The surface of the pellets produced with the new and improved method proved to be smoother.

When comparing the yield of API obtained after the application of the API-containing solution onto the sugar spheres for both studies, a statistically significant difference was observed. The yield of API obtained for the batches produced during this study was higher.

CONCLUSION

Statistical analysis confirmed that the difference between the two set of batches is statistically significant. This implies that the method used for the production of the batches analysed during this study is better and is an improvement over the previously used method.[1]

Acknowledgements

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OBTAINING A MARKETING AUTHORISATION FOR NITROUS OXIDE

Claire Anne Scicluna, Victor Fenech, Lilian M Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida

Corresponding author: Claire Anne Scicluna
E-mail: scicluna.claire@gmail.com

ABSTRACT

OBJECTIVE To prepare a Common Technical Document for nitrous oxide (NO) in accordance to European Guidelines, for submission to the Medicine's Authority to obtain a Marketing Authorisation (MA) and to carry out a project feasibility study.

METHOD Directives and guidelines issued by the European Commission were followed to compile a dossier for NO in the Common Technical Document (CTD) format, in preparation of an abridged application.

KEY FINDINGS The Common Technical Document gave details on the Administrative Information (Module 1), Summaries (Module 2), Quality (Module 3) and Non-Clinical Studies (Module 4) consisting of a detailed scientific bibliography. The active substance manufacturer was inspected and accepted as an approved supplier. A feasibility study which was conducted proved the project feasible.

CONCLUSION The whole manufacturing process of nitrous oxide is well controlled and batches can be produced with a constant level of quality. NO has been used for 150 years for analgesia and anesthesia and has proven safe and effective. Even though its administration is not without risks, it currently has a niche role as an inhalational analgesic and sedative.

KEYWORDS Nitrous oxide, Common Technical Document, Marketing Authorisation

INTRODUCTION

No medicinal product may be placed on the market in Malta unless there is with respect to the product a valid marketing authorisation (MA) issued by the Licensing Authority[1] in accordance with EC Directive 726/2004. The key requirement of an application for a MA is the submission of a dossier.

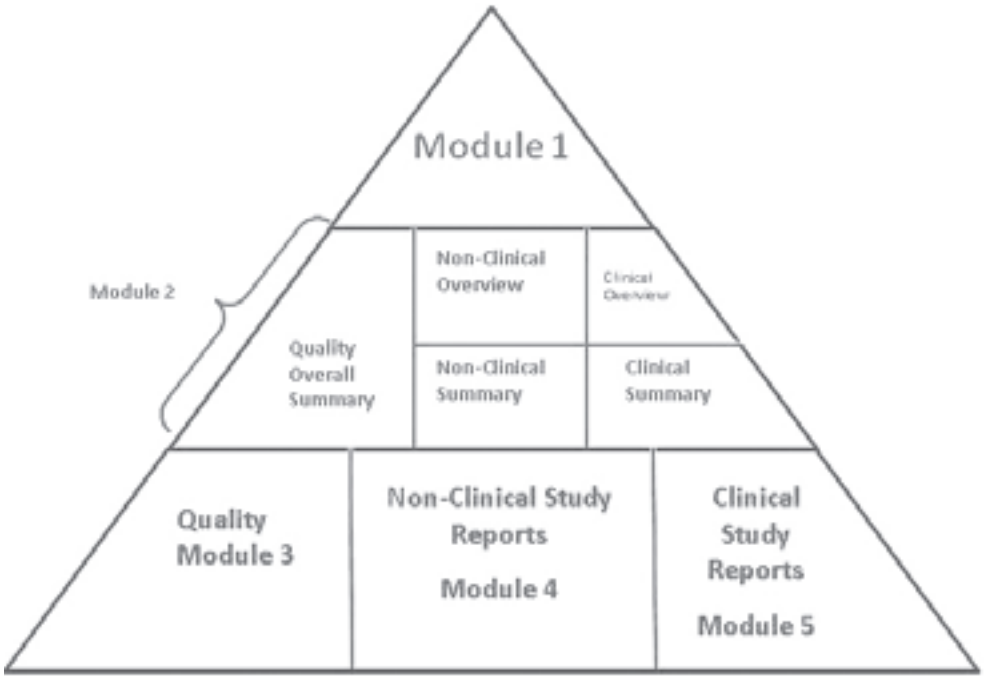

Figure 1 - Common Technical Document format as issued by the ICH

Taken from:
ICH. M4: The Common Technical Document 2004 (cited 2014 Feb 19). Available from: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3_organisation.pdf

The application must be presented in an agreed common format known as the Common Technical Document (CTD), as implemented in July 2003 by the International Conference on Harmonisation (ICH) (Figure 1). Since NO has been widely used in therapeutic practice for several decades and has recognised efficacy and an acceptable level of safety, this medicinal product is defined as having a 'well-established medicinal use' within Article 10(1)(a)(ii) of Directive 2001/83/EC.[2] During initial meetings it was established that the company's intention was to import NO in bulk as the active substance. The NO will be stored at the company's premises in cryogenic tanks and will eventually be used for filling cylinders. Batch release of the finished products will be carried out by the company's Qualified Person after batch analysis. This project aimed at auditing the active ingredient manufacturer and preparing a CTD for an application to obtain a marketing authorisation through a decentralised procedure. Project feasibility was also studied.

METHOD

The official audit of the active ingredient manufacturer consisted of sending an Approval of Suppliers Questionnaire to the potential supplier. The questionnaire was divided into six sections including Personnel, Premises and Equipment, Documentation, Quality Control/Validation, Batch Release, Production/Operation Activities and Maintenance. This was followed by a visit to the manufacturer's premises. An official audit report detailing findings was compiled.

The first undertaking in producing the dossier entailed an exhaustive literature review in which an insight was gathered on different characteristics of NO. The Common Technical Document was compiled according to Notice to Applicants Volume 2B – Medicinal Products for human use as issued by the European Commission in order to fulfil the Commission's obligations with respect to article 6 of Regulation (EC) No. 726/2004[3], and with respect to Annex I of Directive 2001/83/EC.[2] Module 1 included administrative information. Information from the recurrent literature review was used to assemble the Summary of Product Characteristics and Labelling and Patient Information Leaflet. Notice to Applicants – A Guideline on Summary of Product Characteristics issued by the European Commission[4] was used to compile the Summary of Product Characteristics. Guidelines issued by the European Commission - Guideline on the readability of the labeling of and package leaflet of medicinal products for human use, were followed for the compilation of the labeling while guidelines issued by the European Medicines Agency were followed to produce the Patient Information Leaflet.

In accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC[2], a readability study was conducted to ensure the safe use of the medicinal gas. A set of 14 multiple choice questions were compiled. The Patient Information Leaflet and the readability questionnaire were handed to ten participants and the collected data was reviewed. After satisfactory data was obtained a further ten participants were also given the readability questionnaire. Forty percent of the participants were healthcare professionals, 30% were university students and 30% were laypersons. As indicated in Article 56a of Directive 2001/83/EC[2] the name of the medicinal product on the packaging was also expressed in Braille format.

The marketing authorisation for NO will be applied for by an abridged dossier under Article 10a of Directive 2001/83/EC[2] relating to the marketing authorisation of medicinal products with a well established use. In order to demonstrate that NO is a medicinal with a well established use, a literature review was undertaken with respect to the first uses of NO in sedation and anaesthesia. In accordance with Article 8 (ca) and (g) of Directive 2001/83/EC[2] an application for marketing authorisation should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment. Since NO is a greenhouse gas with tremendous global warming potential, literature sources were evaluated and results were drawn up in a report.

A detailed description of the Pharmacovigilance System (DDPS) and an EU Risk Management Plan (EU-RMP) were compiled as outlined in Eudralex Volume 9A.

Test	Specification	Analytical Method
Purity	≥ 98.0% V / V	Infrared
Carbon dioxide	≤ 300 ppm V / V	Gas chromatography
Carbon monoxide	≤ 5 ppm V / V	Gas chromatography
NO + NO_2	≤ 2 ppm	Chemiluminescence
Water	≤ 67 ppm V / V	Electrolytic

Table 1 - Specifications and Analytical Procedures of Nitrous oxide

Taken from:
European Pharmacopoeia version 7.3, Volume 2, Directorate of the Quality of Medicinesof the Council of Europe, 2012. Medicines Conmel Agency

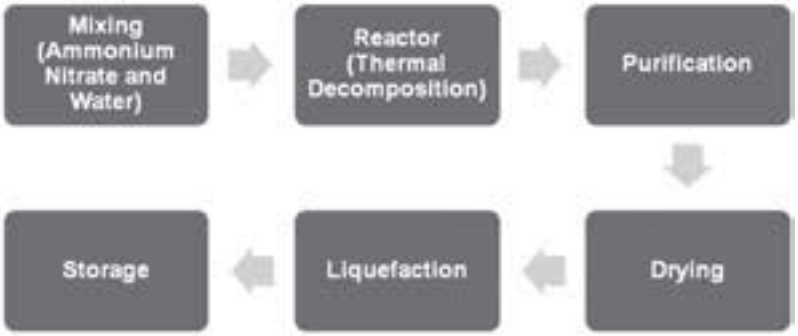

Figure 2: Manufacturing Process of Nitrous oxide

Module 3 – Quality, detailed the quality of the manufacturing process for the active substance and the finished product, including information about the chemical structure, composition, manufacture, quality control, process validation and stability, to demonstrate drug manufacture control and reproducibility.

A retrospective validation study of the production process was carried out by analysing 20 consecutive batches manufactured in 2011. Since nitrous oxide has a 'well-established medicinal use', nonclinical studies (Module 4) consisted of a detailed scientific bibliography giving details on pharmacokinetic, pharmacodynamic and toxicological studies. No clinical trials were carried out hence there was no further information to be presented in module 5. Module 2 contained summaries and overviews of the information presented in detail in the other modules. A market analysis was carried out to establish consumption figures as part of the project's feasibility study. Costs were calculated and the profit and loss schedule was presented. By calculating the return on investment after the first 5 years one was able to determine the feasibility of this project.

RESULTS

The quality system of the Italian manufacturer was deemed acceptable and therefore it was accepted as an approved supplier. In the patient information leaflet readability study, all twelve questions obtained at least sixteen correct answers. Eleven participants rated the length as adequate, thirteen thought the layout is attractive and eighteen considered the letter size acceptable. Nine participants rated the information conveyed as excellent. The well-established use of NO was proven through literature. The environmental risk assessment concluded that the emission levels for NO are very limited and amount to an average of 1.3% of the overall greenhouse gas emissions. Concerns about the environmental impact of the anesthetic use of NO are unfounded as anesthesia accounts for <1% of total NO emissions. The nitrous oxide produced meets the specifications required by the European Pharmacopoeia (Table 1).

The manufacturing process of NO is based on the thermal decomposition of ammonium nitrate through a pyrolysis reaction. The flowchart in Figure 2 shows the main stages of the process. The analytical methods used are those indicated in the European Pharmacopoeia (Table 1). In the manufacturing process validation studies, all batches conformed to the European Pharmacopoeia specifications shown. The minimum and maximum purity results were 99.7% and 99.9% respectively, with a median of 99.97%. The standard deviation values (Table 2) were very minimal. NO is packaged in high pressure cylinders of various sizes, contained at a pressure of approximately 60 bar at 25°C. The different cylinders are identified by their liquid volume ranging from 5 liters or less to 50 liters. Cylinders are made from suitable materials (carbon steel, Cr-Mo steel, stainless steel and aluminum alloys, composite type). Stamp markings as required by European Directives[6] and ISO standards are applied on the cylinders' shoulder.

Parameter	Minimum	Maximum	Median	Std. Dev.	RSD
Purity	99.70 %	99.99 %	99.97 %	0.00064	0.00064 %
CO_2	3 ppm	6 ppm	4.05 ppm	0.94451	23.32 %
CO	1 ppm	1 ppm	1 ppm	0	0 %
NO + NO_2	0.1 ppm	0.2 ppm	0.165 ppm	0.04894	29.66 %
Water	1.1 ppm	3.22 ppm	2.0125 ppm	0.53866	26.77 %

Table 2: Manufacturing Process Validation Statistical Results

The cylinders are fully painted in white with a blue shoulder as per standards and are supplied with two main types of valves; the pin-index valve or the pressure residual valves.

The non-clinical studies included the mechanisms of action of nitrous oxide both as an anesthetic and an analgesic together with its effect on the cardiovascular system, respiratory system, central nervous system, muscle, kidneys, liver and gastrointestinal tract. The known and proposed adverse effects of NO include postoperative nausea and vomiting, megaloblastic anaemia, possible immunosuppression, myocardial ischaemia, increased risk of hypoxia, neural toxicity, possible teratogenicity, expansion of air spaces and increased intracranial pressure. Attention to occupation exposure limits (OELs) is important. Facilities to ensure adequate scavenging and ventilation are imperative to ensure the occupational health of medical staff. Even though, the administration of NO is not without risks, it was proven to be safe and effective through its use throughout the years.

The five year feasibility study proved the project feasible.

DISCUSSION

The audit ensured that the product obtained from that particular site is up to the required quality standard. The visit to the Italian manufacturer also served for training purposes. Training was provided in different aspects of production of NO. This visit took place at an early stage of this project and served as a good introduction to the production process of this medicinal gas. Further training sessions are planned for other company personnel including operators and senior operators.

The readability study concluded that the Product Information presented is legible, clear and easy to use. Through ongoing literature searches and pharmacovigilance activities, new information available will be evaluated and Product Information updated.

Drug manufacture control and reproducibility are essential requirements in Module 3 for reviewers of the Common Technical Document to conclude that the product merits a marketing authorisation. By defining the safety parameters and the critical control steps of both the manufacturing process of the active substance and the manufacturing process of the finished product one ensured that the whole process is well controlled and that the next batch produced is essentially the same as the last batch i.e. batches can be produced with a constant level of quality.

Statistical analysis of data recorded confirms that the process of production of NO is considered to be validated. This feasibility study was conducted by taking into consideration the Maltese market only, which is relatively small and mainly limited to the government sector through a tendering process. Since the company is applying for a decentralised procedure, consumption figures will rise considerably if the company manages to penetrate foreign markets. This will possibly make the project even more feasible.

CONCLUSION

The whole manufacturing process of NO is well controlled and batches can be produced with a constant level of quality.

Nitrous oxide has been used for 150 years for analgesia and anesthesia and has proven safe and effective. Even though its administration is not without risks, it currently has a niche role as an inhalational analgesic and sedative.

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Clinical Pharmacy International Activities at the Department of Pharmacy

On the occasion of an educational visit from students of the College of Pharmacy at the University of Florida, USA the Department organised an International Seminar in Clinical Pharmacy. A total of ten students reading for a PharmD degree, led by Professor Jennifer Williams started their visit to European schools of pharmacy by visiting the Department of Pharmacy at the University of Malta. The event took place between the 8 and the 10 of May 2013.

The Minister for Health, Dr Godfrey Farrugia and the Rector of the University of Malta, Professor Juanito Camilleri welcomed the students from the College of Florida and the participants during the opening session. Professor Lilian M. Azzopardi, Head of Department of Pharmacy at the University of Malta and General Secretary for the European Association of Faculties of Pharmacy presented an introduction into developments in pharmacy education in Europe. The seminar consisted of a number of workshops which included sessions at Mater Dei Hospital and patient interviews and discussions on aspects of clinical pharmacy education and clinical pharmacy service provision in Malta, in the USA and internationally. Professor Serracino Inglott presented developments in pharmacy education and research in Malta including an insight into historical aspects related to local pharmacy practice. Research studies in the area of clinical pharmacy which are currently being undertaken within the Department of Pharmacy were presented by pharmacy students and postgraduate students. The topics presented included Patient Management and Treatment in Rheumatology, Risk Management in Pharmacy, Patient Management in Cardiovascular diseases. The variety of topics presented the students from both Universities with an opportunity to discuss the latest and most upcoming aspects of clinical pharmacy.

An international pharmacy students evening was organised by the Malta Pharmaceutical Students Association and this provided the opportunity for the students from Florida, pharmacy students from European Universities who are currently in Malta on an Erasmus mobility and pharmacy students and faculty from the University of Malta to interact in an informal setting with the Valletta harbour as a historical background.

The Seminar provided an opportunity for the students from Florida to experience clinical pharmacy developments in Malta and to understand our cultural and historical roots. It was an opportunity for students from the University of Malta to share their experiences and discuss aspects related to the progress of clinical pharmacy, such as the development of an international curriculum for clinical pharmacy, within an international perspective.

The one week intensive clinical pharmacy course for five pharmacists following a postgraduate course in clinical pharmacy at the University of Bari was organised for the third consecutive year in June 2013 at the Department of Pharmacy. The clinical pharmacy course was led by Lilian M. Azzopardi, Head of the Department together with academics, research staff and students from the Department of Pharmacy and the Faculty of Medicine and Surgery. Pharmacists Alison Anastasi, Maresca Attard Pizzuto, Marise Gauci, Louise Grech, Anthony Serracino Inglott and Francesca Wirth from the Department were course tutors. During the course, the Italian pharmacists had the opportunity to participate in supervised clinical pharmacy activities including ward rounds and outpatient clinic visits. The course was held at the Cardiology, Medicine and Rheumatology Departments at Mater Dei Hospital and at Karin Grech Rehabilitation Hospital. At the end of the course, the Italian students prepared and discussed patient case presentations identified during ward rounds during a seminar where course tutors and pharmacy practice tutor practitioners participated in the discussion.

Malta Pharmaceutical Students Association

MPSA

The Malta Pharmaceutical Students Association -MPSA- is constantly growing and evolving as an organisation. Each year, new initiatives are taken to help pharmacy students reach ever growing goals.

This year it was decided to represent MPSA virtually. A new website, hosted specifically to keep our members updated on current events was created and launched. The website also serves as a platform where students can ask queries and learn from each other.

Apart from representing the student body at a University level, MPSA strives to represent pharmacists on a national level. MPSA aims at educating people and increasing national awareness of the important role of the pharmacist in the community.

MPSA's Health Campaigns Team continuously strives at achieving this goal. A large number of pharmacy students participated actively in various events organised by MPSA, with the help of various sponsors and other local organisations such as the Malta Pharmaceutical Association, the Malta Chamber of Pharmacists and the University of Malta's Department of Pharmacy. One of the most successful events organised to date is the World Pharmacists Day spanning over the entire week of the 23rd to the 27th of September. This campaign was held in several localities in Malta including Valletta, Sliema so as to reach as many people as possible. Approximately 40 students volunteered to participate in this event. Each student asked passers-by if they were willing to fill in a short questionnaire regarding their perception of the pharmacist. An informative leaflet describing the pharmacist's profession and their role in the community, research, industrial and clinical settings was disseminated. MPSA participated actively in other activities including Science in the city, World Osteoporosis Day and World Diabetes Day.

MPSA is an active member of both the European Pharmaceutical Students Association (EPSA), as well as the International Pharmaceutical Students Federation (IPSF).

IPSF represents more than 350,000 pharmacy students and recent graduates in 84 countries worldwide. IPSF is a non-profit, non-political and non-religious volunteer organisation.

IPSF is the leading international advocacy organisation of pharmacy students promoting improved public health through provision of information, education, networking, and a range of professional activities. The Student Exchange Program (SEP) has allowed students from IPSF member organisations as well as IPSF individual members to explore and learn pharmacy in other countries since 1958. Currently, close to 60 associations throughout the world participate in SEP and over 600 international exchanges take place every year. MPSA is proud to host students from SEP during the summer months. This year, over 50 applications have already been received by MPSA from different countries including USA, Poland and Serbia.

World Pharmacist Day - Blood Pressure Testing

EPSA, which has been a leader in bringing pharmacy, knowledge and students together for more than 35 years, represents more than 160,000 pharmacy students and recent graduates in 36 countries across Europe. EPSA is a volunteer-based non-profit and non-political student organisation working in the interest of European pharmacy students.

Recently, MPSA has also placed a bid to host the 2015 Autumn Assembly, where up to 400 European students could be hosted. The Autumn Assembly is the second biggest annual event organised by EPSA. It provides an opportunity for EPSA members to review the work of the association half way through the mandate and at the same time to renew motivation and commitment to EPSA.

MPSA works and interacts with as many students as possible. By motivating students to work together as part of the team, MPSA lives on.

Istanbul- Turkey Quattrino Project

Osteoporosis Day - Group Photo

Autumn Assembly 2013 in Valencia

AUTHOR GUIDELINES

Manuscript Preparation

All contributing authors should include their full name, affiliation at time of running the study, postal address, telephone and fax numbers and email address on the title page of the manuscript. One author should be identified as the corresponding author.

Manuscripts should include title page, abstract, text, references, tables and figures. The pages of the manuscript must be numbered.

Manuscripts should not exceed 2000 words (including abstract and references, excluding title page, tables and figures).

Abstract

The format for the abstract is structured and should include objectives, method, key findings and conclusion.

Keywords

Three to five keywords should be provided.

Introduction

The introduction should provide a background to the study and should clearly state the aims of the study. Provide a definition for any abbreviations and symbols that are used.

Methods

This section should describe the subjects, setting and methods in sufficient detail to allow possibility of replication of the study. Include details of ethical approval, if applicable, in this section.

Results

This section should present the salient results of the study. Epidemiological description of sample population, where relevant, and details of response rates should be provided. Data should not be repeated in figures and tables. Describe statistical analysis undertaken.

Discussion

In the discussion a summary of the main findings of the study is to be presented and these are to be discussed in the context of international published literature and contributions to the field. Limitations and strengths of the study should be highlighted.

Conclusion

A brief conclusion section should summarize the prominent findings of the study. It is advisable to emphasize the contribution to the field of study by the current findings.

Acknowledgements and funding

Any funding received for the study should be declared in this section.

References

References should be listed in numerical order as they appear in the text. All citations in the text must have an entry in the reference list and vice versa. All the reference numbers in the text should be in superscript.

The references should be listed at the end of the manuscript according to the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Please see http://www.nlm.nih.gov/bsd/uniform_requirements.html

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Maximum of a total of 4 tables and/or figures.

Tables and Figures should be numbered consecutively and each must start on a separate page at the end of the manuscript. Graphs, pie charts, figures and tables are to be supplied separately on Excel and as pdfs.

Each table and figure must have a title. Define any abbreviations used. If values are cited in a table or figure, the unit of measurement must be stated.

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