

# JEMP

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OF EUROMED  
PHARMACY



CLOZAPINE  
TREATMENT  
IN PATIENTS  
LIVING IN THE  
COMMUNITY

PERCEPTION  
AND CRITICAL  
ANALYSIS  
OF THE MEDICINES  
ENTITLEMENT  
SYSTEM

THE  
RELATIONSHIP  
BETWEEN  
BIOLOGICALS AND  
INNOVATION



Pharmacist working on Treatment Protocol

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\*as part of a project being carried out in partial fulfilment of the requirements of the course leading to a degree in pharmacy.

**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.

## TREATMENT PROTOCOLS

Protocols are a valuable tool in supporting pharmacists in the provision of care specific to the needs of a particular population. Protocols lead pharmacists through a therapeutic plan to take evidence-based decisions to select the most appropriate medications for their patients. Pharmacists are often approached by patients and other healthcare professionals for advice on a number of problems. The availability of protocols helps pharmacists to make a rational recommendation. In order for protocols to be a valuable tool in supporting pharmacists in the provision of care specific to the needs of the population, they need to be reviewed, updated and validated by a panel of healthcare professionals. The process of protocol development should include an evaluation to confirm that they are practical for use and user friendly. The various steps recommended in a protocol should be evidence-based. Protocols may also be structured to provide guidelines on the correct and effective use of non-prescription medicines.

Students within the Department of Pharmacy have developed a number of protocols throughout the years as part of their studies. These include protocols for paediatric care, dental conditions, management of urinary tract infections during pregnancy, gastrointestinal disorders, eye conditions and the common cold. These protocols were used by the students to investigate their applicability and practicality and to evaluate the use of the protocols as training tools for pharmacy students. Methods to disseminate and encourage compliance with protocols were also investigated and the results are presented in students' projects. The projects are available at the Department of Pharmacy at the Tal-Qroqq Campus.

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.



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## EDITORIAL

# SCHOLARSHIPS FOR ADVANCED STUDIES IN PHARMACY

The need for pharmacy education to keep up with developments in the fast world of science and practice is now accepted as urgent on the pharmacy agenda. One needs to innovate a philosophy for tomorrow's pharmacy. Such philosophy should include concepts as the evaluation and containment of adverse risks of drug therapy and pharmaceutical processes. The will of pharmacists from all parts of the world to further their education is there. The facilities to do so with excellence are being provided. Ways of enabling these bright pharmacists to achieve these goals from a financial point of view are proving to be more difficult.

The Department of Pharmacy of the University of Malta has started an innovative post-graduate Level 8 International Doctor of Pharmacy Course last October in collaboration with the University of Illinois at Chicago (USA). Scholarships in the form of paid placements in different areas are available for both local and international candidates. These placements are provided in consultation with established entities and institutions such as the Chamber of Commerce and the Medicines Authority. The research component of the course is tailor-made to meet with the individual aspirations and capabilities of the candidates. The experience gained during the past months, now that eighteen candidates have completed the first semester, is very encouraging as can be evidenced through reading their reflections published in this issue of the JEMP.

The Department of Pharmacy through this course is providing the local and international pharmacists with a rewarding and fruitful unique experience. Through the prestigious and enthusiastic faculty of the University of Illinois at Chicago, an international flavour is given to the course. Quoting a number of phrases expressed by candidates themselves is possibly the best and true form of describing some characteristics of this course. The following are some phrases used by the Doctor of Pharmacy candidates to describe the course: "holistic view of pharmaceutical care, full immersion practice-based clinical experience, emphasis for clinical research and evidence-based practice, strategic management of services, better understanding of systems and structures supporting pharmaceutical services, practicing within multidisciplinary teams, mixed learning approach, flexibility, particularly of benefit to mature students returning to their studies, in-depth volume of taught material, insight to key areas, improve critical thinking and problem-solving skills, improving knowledge, better perspective on different healthcare systems, policy

and practice in local and international settings, strengthen skills such as communication abilities, enabling oneself to broaden the knowledge and gain more experience, course is innovative in the way lectures are given".

The candidates also stated that the course offers good prospects for career paths in clinical specialisation, strategic management of pharmaceutical care delivery systems and processes, as well as training in tutoring and provides practicing pharmacists who would like to improve their career with optimal tools.

Another course started recently by the Department of Pharmacy that is attracting a number of students, is the Bachelor of Science in Pharmaceutical Technology. Malta has a strong pharmaceutical industry mainly concerned with the production of generic medicines. This flourishing industry is supported by graduates from the Department of Pharmacy. A strong contribution by the local pharmaceutical industry is in the area of release of pharmaceutical products manufactured in third countries, such as India, to the European market. These developments are all the more possible because Malta has a very strong regulatory affairs ethos including a well-structured Medicines Authority. This authority is also involved, in addition to its duties in the local scenario, in the carrying out of third country GMP inspections and evaluation of centrally registered products. A number of students from the Department are involved in these areas including those following the Bachelor of Science in Pharmaceutical Technology programme.

The Department has a strong research programme supported by a number of PhD students and full-time graduate research support officers. Examples of these projects are 'Innovative tools to investigate risk in pharmaceutical processes', 'New pathways for development of synthetic steroids', 'Distribution of anti-infective agents in the peripheries' and 'Pharmacogenetic implications in clopidogrel therapy: A pharmacist-led management approach'.

Those interested to join the Doctor of Pharmacy course or the Bachelor of Science in Pharmaceutical Technology may contact the course co-ordinator Professor Lilian M. Azzopardi at the Department of Pharmacy of the University of Malta, email: [lilian.m.azzopardi@um.edu.mt](mailto:lilian.m.azzopardi@um.edu.mt); website: <http://www.um.edu.mt/ms/pharmacy>.

*Professor Anthony Serracino-Inglott*

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# JOINING THE PROFESSIONAL DOCTORATE IN PHARMACY



Want to develop your skills in advanced clinical pharmacy? Interested in furthering your studies at a Doctorate level? Then consider joining the Professional Doctorate in Pharmacy!



## 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 contextualisation 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.

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# PHARM D STUDENTS' REFLECTIONS

## RICHARD DESPOTT

The course has a very broad scope and has therefore provided a holistic view of pharmaceutical care, which is most interesting at a personal level with regards to strategic management of services. The majority of course material is oriented at clinical specialisation.

The mixed learning approach in the Pharm D. programme greatly enhances professional development as it provides access to foreign tutorship (via teleconferencing) with different skills and styles, flexibility (recorded lectures on the Virtual Learning Environment) and full immersion practice-based clinical experience. The approach is stimulating and delivers a broad and in-depth volume of taught material. With the online lectures, students may benefit from more time allowed for preparing lecture notes, revising technical concepts and background, carrying out research to complement the text or digest the material provided, particularly mature students who are returning to their studies after a number of years.

The course provides a strong emphasis on clinical research and evidence based practice, as well as an advanced insight to key areas (particularly health systems at a personal level) where research studies can contribute to improving healthcare delivery. The course also provides a deeper appreciation of the potential offered by clinical pharmacy services and better understanding of the systems and structures needed to support these services.

In my view, the course offers good prospects for career paths in clinical specialisation, strategic management of pharmaceutical care delivery systems and processes, as well as tutoring. In view of the fact that this is the first intake, feedback from students on the details of course dynamics may be useful to enhance the experience and outcome.

## ALISON ATTARD

I have just finished my first semester in the Doctorate of Pharmacy course and although it was very intense I must admit that it was one of the best educational experiences I have ever had.

As a working pharmacist with family obligations, it was very interesting to see how this course offers flexibility in the sense that most of the lectures were via online teaching. We also had live recitations from experienced specialists from various areas who gave us the opportunity to discuss and apply the knowledge from the online sessions to real case scenarios. These practice scenarios helped me improve my critical thinking and problem-solving skills while increasing my knowledge in areas such as pharmacotherapeutics. This programme also offers the opportunity for students to have a broader perspective regarding different healthcare systems, policy and practice in local and international settings.

I really enjoyed my first clinical rotation in a local Rehabilitation Hospital where clinical pharmacists have the opportunity to intervene in patient care by managing and improving the medication use process. The interventions carried out by clinical pharmacists were always evidence-based with a patient-centred approach within multidisciplinary teams.

I am sure that this course will not just enhance my professional competence but will also help me develop leadership skills in pharmaceutical service development. It is definitely the next step for practicing pharmacists who would like to improve their career.



## **This course will not just enhance my professional competence but will also help me develop leadership skills in pharmaceutical service development.**

### **ROBERTA AGIUS**

The Pharm D. program provides an exceptional teaching and learning environment for pharmacists to enhance their knowledge and practice skills in performing the pharmacist's role in health care delivery. The mixed learning approach which includes lectures, distance learning and practise based learning such as clinical rotations, is a new concept which is the major contributor to a collaborative learning experience. The distance learning lectures and live recitations which take place with specialised pharmacists from the University of Illinois in Chicago, is a unique experience which gives us a great opportunity to learn and discuss the latest updates which are taking place in the pharmaceutical sector.

This course is giving me an opportunity to strengthen skills such as communication abilities, critical thinking and decision-making, management of medication knowledge and support decision-making using appropriate information sources and technology, inter-professional collaborative practice, patient pharmacotherapy assessment, plan and management. This will enable me to advance in my career and be more confident in assuming leadership roles in the management of pharmaceutical care. I highly recommend this course to other potential candidates so that we, as pharmacists, can enhance our contribution in all pharmaceutical areas including clinical pharmacy, community pharmacy, regulatory affairs, pharmaceutical industry and research and development.

### **NOELIA HELGADO SANCHEZ**

I find that the lectures are very interesting and cover several clinical scenarios. I believe that the course is highly educational as well as innovative in the way lectures are taught. Lectures taught via video-conferencing are interactive and highlight the level of organisation and excellent communication between the University of Malta and University of Illinois in Chicago.

### **DANIKA AGIUS DECELIS**

The triangulation teaching approach gives a broader picture and knowledge of how to deal with situations via multiple approaches. The course, being segmented as it is, helps to add more dimensions to the ability to improve patient care and exposes us to different learning techniques while giving us a more holistic approach. These are areas one would not have covered had the programme been simply based on research.

Education is not the learning of facts but the training of the mind to think. This is the precise tool that is passed on to us from this course. The Pharm D. programme demonstrates how pharmaceutical issues are handled in other countries. It gives a different perspective to various issues and it also allows one to think on a completely higher level, enabling oneself to broaden the knowledge, gain more experience and learn from others.

Pharmacists are the bridge between patients and other health care professionals. With this tool in hand one can be able to integrate the knowledge and experience gained and use it both at administrative and policy-making levels as well as a clinical level, always keeping the patient's interests a priority. It gives more status to the profession while working in a multidisciplinary team at all levels.

I will definitely recommend the course to other potential candidates. Education is our passport to the future. Although it requires a lot of sacrifices, it is definitely worth it at the end.

### **KHALED ABDELMAULA**

I believe that the course will be an asset for my career in pharmacy due to the variety of subjects covered whilst getting an extensive view of healthcare systems. This is emphasised by the contribution of foreign lecturers who give us an idea of the international scenario.

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# CLOZAPINE TREATMENT IN PATIENTS LIVING IN THE COMMUNITY

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## ABSTRACT

**OBJECTIVE** The aim of this study was to assess clozapine treatment in the local community with respect to patient monitoring during dispensing, patient compliance through prescription refills, presence of any other existing co-morbidities and presence of potential drug-drug interactions.

**METHOD** An audit on whether pharmacy personnel check patients' white blood cell count and absolute neutrophil count prior to dispensing was performed. A total of 100 audits were carried out. A computer programme entitled 'Pharmacy Dispensing System' was used to assess patient compliance through prescription refills over a 3-month period. Another computer programme entitled 'Schedule V' was used to determine any other co-morbidities. After determining the list of all the chronic medications, analysis of the presence of any potential drug-drug interactions was undertaken. The 'Drug Interaction Checker', a drug interaction database provided by RxList, was used. This database classified potential drug-drug interactions into 3 categories namely minor, significant and serious.

**KEY FINDINGS** The white blood cell count and absolute neutrophil count were checked in all instances (N=100), however this intervention was not documented. Over a 3-month period, 78 out of 90 patients were compliant. Diabetes was the most common co-morbidity (n=15) and 76 patients receiving clozapine may be exposed to a potential drug-drug interaction. A total of 363 possible drug interactions were present in this group of patients. The most common type of potential drug-drug interaction fell in the 'significant drug-drug interactions' category (n=289).

**CONCLUSION** Patient monitoring was carried out, however documentation processes need to be elaborated. Identification of drug interactions is of utmost importance since certain interactions can be dangerous. Apart from detecting drug interactions, discussion with other healthcare professionals should be undertaken to assess the possibility of replacing such interacting drugs with alternative options. This measure should be carried out to promote patient safety.

**KEYWORDS** clozapine, patient monitoring, co-morbidities, drug-drug interactions

## INTRODUCTION

Clozapine is an atypical antipsychotic used in treatment-resistant schizophrenia.<sup>1</sup> In Malta patients who are on this drug and live in the community collect this medication from the Outpatients Pharmacy at Mater Dei Hospital. The maximum supply of clozapine dispensed is for 28 days. Since clozapine causes agranulocytosis<sup>2</sup>, the white blood cell count and absolute neutrophil count have to be checked prior to dispensing. The occurrence of potential drug-drug interactions is quite common in psychiatric patients since a large number of antipsychotics are metabolised through the hepatic cytochrome P450 system.<sup>3</sup>

The aim of this study was to review clozapine treatment in patients living in the community with respect to undertaking of patient monitoring during dispensing, assessment of patient compliance to clozapine treatment through prescription refills, determination of the presence of any other co-morbidities and assessment of the presence of potential drug-drug interactions.

## METHOD

Approval to carry the study was obtained from the Chief Executive Officer and the Head of the Pharmacy Department at Mater Dei Hospital, as well as the Data Protection Officers of both Mater Dei Hospital and the Directorate of Pharmaceutical Affairs.

A form entitled 'Audit Form for Patient Monitoring' was designed to evaluate patient monitoring. Observation of whether the pharmacist or pharmacy technician dispensing clozapine checked the white blood cell and absolute neutrophil count was undertaken. Another procedure observed was whether the pharmacist in charge of the high security store carries out double checking with regards to the mentioned parameters in the complete blood count. The audit was repeated 100 times.

Since compliance to clozapine was assessed through prescription refills, the computer programme entitled 'Pharmacy Dispensing System' was used. This programme is useful since it keeps records of any medication collected from Mater Dei Hospital. Clozapine compliance was retrospectively assessed over a 3-month period.



The Schedule V program is a computer programme which can be used to determine the list of chronic conditions the patient is suffering from. The number of co-morbidities present in each patient and the number of patients suffering from a particular co-morbidity was obtained. The medicines entitlement was used to obtain any other chronic medication/s the patient was taking during the selected 3-month period. After determining the list of medications, analysis for the occurrence of any potential drug-drug interactions was carried out. The drug interaction database used in this study was the 'Drug Interaction Checker' provided by RxList.<sup>4</sup> The frequency of patients experiencing a potential drug-drug interaction and the mean number of potential drug-drug interactions occurring in each patient were determined. The drug interaction database classified such potential drug-drug interactions into 3 categories, namely minor, significant and serious. The total number of potential drug-drug interactions and the total number of potential drug-drug interaction combinations in each category were determined.

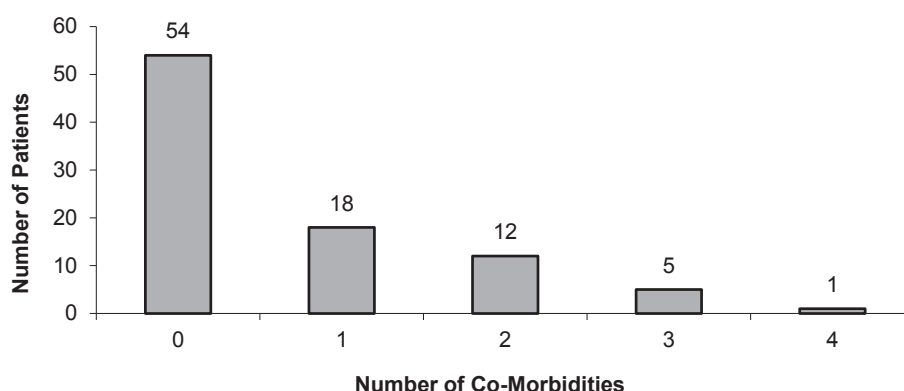
## RESULTS

The white blood cell count and absolute neutrophil count were checked in all instances (N=100) by the pharmacist or pharmacy technician dispensing the medication, as well as by the pharmacist in charge of the high security store.

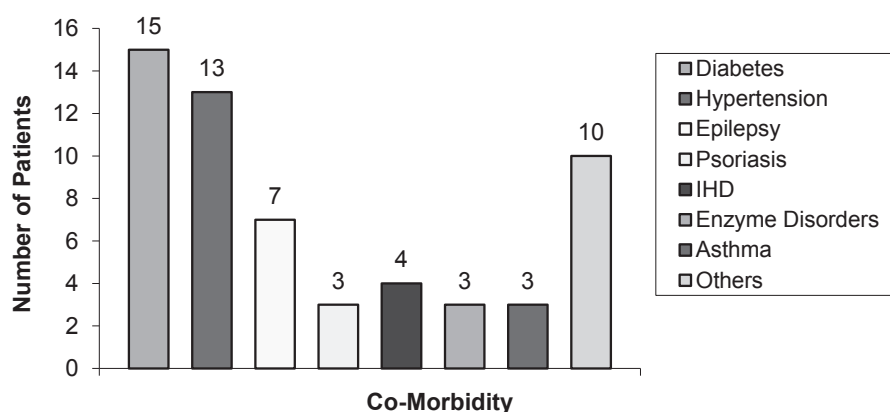
A total of 90 patients were included in the study, where 47 were female and 43 were male. The mean age of the patients was 50 years (range 20-80 years). Patient compliance to clozapine was assessed through prescription refills, where 78 out of 90 patients were compliant. The majority of patients (n=54) did not suffer from any other co-morbidities (Figure 1).

The most common (n=15) co-morbidity present was diabetes (Figure 2). The co-morbidities classified as 'Others' included gastro-oesophageal reflux disease (n=1), hypoparathyroidism (n=1), genetic dyslipidaemia (n=2), peripheral vascular disease (n=1), gastric ulcers (n=2), arrhythmias (n=1), myasthenia gravis (n=1) and cerebrovascular disease (n=1).

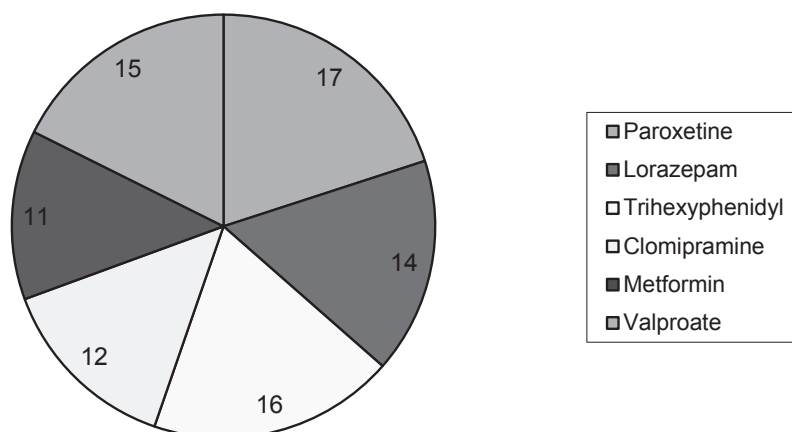
The most common drug taken by the patients in combination with clozapine was paroxetine (n=17) (Figure 3).



**Figure 1:** Number of co-morbidities present in clozapine-treated patients (N=90)



**Figure 2:** Frequency of the different co-morbidities in clozapine patients living in the community (N=90)



**Figure 3:** Frequency of the 6 most common drugs taken together with clozapine (N=90)

A total of 363 potential drug-drug interactions were identified in these patients. Out of 90 patients, 76 patients could be exposed to drug interactions. The mean number of potential drug-drug interactions present in each patient is 4. 'Significant' drug-drug interactions (n=289) are the most common type of potential drug-drug interactions. This is followed by 'minor' drug-drug interactions (n=54) and 'serious' drug-drug interactions (n=20).

## DISCUSSION

Even though the white blood cell and absolute neutrophil count were checked in all instances, this intervention was not documented. Documentation of an intervention is important since it provides a way for the pharmacist to be responsible for his or her actions. It also provides a means of communication with other healthcare professionals during the planning of patient care. Documentation must be complete, factual, current, and organised.<sup>5</sup> The computer programme 'Pharmacy Dispensing System' can be used to document this intervention to ensure that good documentation is maintained. The person dispensing the medication can document this process under the remarks section by writing the values for the white blood cell and absolute neutrophil count and whether the values are within the required limits. When the transaction is complete, a sticker with this information, together with the amount of medications dispensed, is produced and fixed on the back of the patient's Schedule V Card. The professional dispensing the medication can sign on this sticker, followed by a counter signature by the pharmacist who double checks this intervention. This procedure would ensure that the patient and health care professionals who view the patient's Schedule V card would be aware that the patient's white blood cell and absolute neutrophil count are being monitored.

There are various reasons which explain the reason for diabetes being a common occurrence in schizophrenic patients. Clozapine has various side-effects including hyperglycemia, weight gain, hypercholesterolemia and hypertriglyceridemia.<sup>6</sup> These side-effects increase the patient's risk of developing diabetes. Another reason why diabetes is the most common co-morbidity is that there is a relationship between schizophrenia and diabetes. It has been found that schizophrenic patients are 2 to 4 times more likely to develop diabetes.<sup>7</sup> Another factor which contributes towards a high incidence of diabetes mellitus is the high occurrence of diabetes in the Maltese population.<sup>8</sup> The pharmacist should therefore monitor the patient for diabetes mellitus during dispensing.

The occurrence of potential drug-drug interactions may lead to the need for hospitalisation. A study by Raschetti *et al* has shown that the frequency of visits to the emergency department due to drug-drug interactions represented 3.8% of the total visits.<sup>9</sup> Having a clinical pharmacist assigned to psychiatric consultants is recommended to reduce the potential occurrence of drug-related problems and to provide information about interactions to physicians and patients. At present, there are no clinical pharmacists forming part of the psychiatric team at Mater Dei Hospital. Pharmacists are in an ideal position to give advice about the occurrence of potential drug-drug interactions.

A limitation of this study was the method chosen to determine patient compliance. The determination of the rate of prescription refills is not expensive and easy to carry out, however, this method is not as accurate as direct observation of patient compliance to treatment. Another limitation was that only chronic drugs which are collected for free were considered for the occurrence of potential drug-drug interactions. Drugs which the patient might purchase were not included.



## Having a clinical pharmacist assigned to psychiatric consultants is recommended to reduce the potential occurrence of drug-related problems and to provide information about interactions to physicians and patients.

### CONCLUSION

Patient adherence to medication is necessary to achieve the maximal therapeutic benefit. Since certain drug-drug interactions can be dangerous, it is important that interactions are detected. Besides detecting drug-drug interactions, discussion with other healthcare professionals regarding clozapine treatment and therapies used for co-morbidities should be carried out to assess the possibility of replacing the interacting drug with alternative treatment options. The introduction of such a procedure will help to further promote patient safety.

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# PERCEPTION AND CRITICAL ANALYSIS OF THE MEDICINES ENTITLEMENT SYSTEM

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## ABSTRACT

**OBJECTIVES** To determine the perceived, actual and desired knowledge of healthcare professionals regarding free medicines' entitlement, to identify strengths and weaknesses of the present entitlement system and to recommend improvements to the system to enhance patient care and sustainability.

**METHOD** Qualitative interviews with the Medicines Entitlement Unit (MEU) staff were carried out to identify customer care-related issues encountered. This information was used to devise a questionnaire to assess perceived, actual and desired knowledge on medicines' entitlement. The questionnaire was distributed to physicians, pharmacists and pharmacy technicians. A strengths, weaknesses, opportunities and threats analysis of the medicines' entitlement system was undertaken through qualitative interviews.

**KEY FINDINGS** A total of 26 strengths, 7 weaknesses, 6 opportunities and 15 threats on the present entitlement system were identified during the discussion sessions with 20 participants. Strengths included legislation, reference documentation and customer care service while the main weakness identified was the current IT system. Opportunities included an improved IT system and premises. Threats identified included manual applications, misconceptions by the public and healthcare professionals and patients' attitudes and expectations. A total of 207 physicians, pharmacists and pharmacy technicians from different professional backgrounds completed the questionnaire. The participants obtained an average score of 72.2%. The respondents obtained a significantly higher mean score ( $p < 0.001$ ) for questions related to Fifth (V) Schedule conditions and entitlement (81.60%), compared to the mean score for the questions related to the Government Formulary List (GFL) and related policies (63.57%). Pharmacists obtained a significantly ( $p = 0.005$ ) higher total mean score (75.89%) than physicians (66.21%). A positive relationship between the self-rating and actual overall knowledge was found; the mean total scores vary significantly between the overall knowledge self-rating ( $p < 0.001$ ).

**CONCLUSION** The results show that healthcare professionals have appropriate insight of the medicines' entitlement system and are very interested in improving their knowledge. Measures to increase their knowledge should be considered. The weaknesses and opportunities identified should be addressed to improve the current entitlement system both for the patients and healthcare professionals.

**KEYWORDS** Critical Analysis, Medicines Entitlement, Government Formulary List

## INTRODUCTION

In Malta free medicines entitlement is in accordance with the Fifth Schedule of the Social Security Act Chapter 318 Article 23 and the amendment of this Act of 2012 and 2014.<sup>1,2</sup>

Since in Malta free medicines' entitlement is based on the presence of disease and is irrespective of income or age, any patient suffering from any one (or more) of the conditions listed in the Fifth Schedule, is entitled to free treatment for that specific disease.<sup>3</sup> Patients are entitled to free treatment available on the Government Formulary List (GFL) and entitlement is provided once it is in line with GFL policies. In this paper, any reference to the term GFL includes both the Out-Patients' Formulary and Hospital Formulary.

Patients suffering from any one or more of these conditions are entitled to a Schedule V card, which is colloquially known as the 'yellow card'. A patient holding a Schedule V card is only entitled to those medicines listed on the card. Some of the medicines are also further regulated with a protocol, for example as is the case for, atorvastatin.

The Medicines Entitlement Unit (MEU) is responsible for processing Schedule V Card applications and Protocol Regulated Medicines applications and issuing of Schedule V Cards and permits.

The aims of this project were to determine the perceived, actual and desired knowledge of healthcare professionals regarding free medicines' entitlement, to identify strengths and weaknesses within the present entitlement system and to recommend improvements in the system to enhance patient care and sustainability.



## METHOD

Approval from the Director of the Directorate for Pharmaceutical Affairs (DPA) was granted. All pharmacists and pharmacy technicians working within the DPA were invited to participate in the study. Analysis to identify the strengths, weaknesses, opportunities and threats (SWOT) was carried out in the form of qualitative group discussions with the staff who agreed to participate. The methodology used to carry out the SWOT analysis in this study was based on the methodology used by Cassar in 2012.<sup>4</sup> The reference and policy documents used by the MEU staff such as formularies and protocols were evaluated.

Qualitative interviews with MEU staff were also carried out to discuss and highlight several misconceptions and queries encountered during customer care. Information obtained from these interviews was used to draw up the questionnaire used to determine the perceived, actual and desired knowledge of healthcare professionals on medicines' entitlement. The questionnaire included questions related to the Government Formulary list and its related policies and also questions on Schedule V conditions and entitlement procedures. The respondents were rated on the correct responses to the 23-item questionnaire. The questionnaire was subsequently distributed manually and electronically to physicians, pharmacists and pharmacy technicians and the results obtained were analysed using Microsoft® Excel 2013 and SPSS® version 22.

## RESULTS

All 14 pharmacists and 6 pharmacy technicians working within the DPA agreed to participate to identify the strengths, weaknesses, opportunities and threats.

A total of 8 discussion sessions were carried out, each session lasted approximately 40 minutes. A total of 26 strengths, 7 weaknesses, 6 opportunities and 15 threats on the current entitlement system were identified.

Identified strengths include: the Medicines Entitlement system is backed up by legislation, use of reference documentation to process the applications in a transparent and equitable way, availability of customer services, availability of various methods to submit applications, continuous efforts are made to increase the information

about the Medicines' Entitlement System and its processes, and certain processes were made more flexible to reduce bureaucracy.

Weaknesses included the current IT system which is very out-dated, free medicines entitlement is limited to 79 conditions, the website is not user-friendly, some changes are not advertised properly, open treatment with certain Schedule V cards and certain applications are not straightforward due to the particular situation of the patient and information provided. Opportunities included a new IT system, better premises, more awareness on the entitlement system, reduction in bureaucracy, access of entitlement databases to healthcare professionals and one stop shop with POYC. Threats identified are the location of the MEU premises, the use of manual applications, misconceptions on the system by the public and healthcare professionals, patients' attitudes and expectations, the fact that sometimes patients are not seen by clinicians when reviewing entitlement documents and also that private family doctors and physicians in the private healthcare system cannot apply for entitlement documents.

The staff at the MEU use 6 reference documents, namely; out-patients formulary, hospital formulary, government protocols, formulary mapping document, Standard Operating Procedures on MEU processes and MEU working guidelines. The MEU staff stated that they found these documents useful and use them regularly. Certain amendments were suggested, such as improving the user-friendliness of the formularies.

A total of 207 healthcare professionals answered the questionnaire, of which 123 were pharmacists, 57 were medical doctors and 27 were pharmacy technicians.

The majority of the doctors answering the questionnaire worked in hospital (n=23), the majority of the pharmacists worked in community (n=46) and most of the pharmacy technicians worked in procurement and supplies (n=6). With regards to knowledge of entitlement system by respondents, a mean score of 72.2% was obtained. Participants obtained a significantly higher mean score on Schedule V related questions when compared to the mean score on questions related to the GFL (Table 1). The paired samples t-test showed a p-value of approximately zero, hence implying that they are more knowledgeable on Schedule V conditions and related entitlement.

	Mean (%)	N	Std. Deviation	Std. Error Mean
Scores of Schedule V related questions	81.60	207	19.99	1.32
Scores of GFL related questions	63.57	207	25.77	1.79

$t(206) = 11.89, p < 0.001$

**Table 1:** Paired Samples t-test

The one-way ANOVA test was used to compare the mean percentage scores between independent groups (Table 2). Pharmacists got a significantly higher mean score (70.19%) for the questions related to the GFL with a p-value of approximately zero. Physicians got a marginally higher score (82.78%) for questions related to Schedule V and entitlement. Pharmacists obtained a significantly higher overall mark (75.89%) with a p-value of 0.005.

'Very Knowledgeable' was the highest (88.79%). There is a statistically significant relationship between the self-rating and the actual overall knowledge, with a p-value of approximately zero. The majority of participants (n=195) answered that they would like to increase their knowledge. Information through email updates were the preferred choice (n=159), followed by website (n=91) and information sessions/lectures (n=70).

The respondents were asked to rate their knowledge on the Medicines' Entitlement System (Table 3). The total mean score obtained by participants who rated themselves as 'Not Knowledgeable' was the lowest (16.15%) and the mean score of the participants who rated themselves as

		Mean (%)	Std. Deviation	95% Confidence Interval for Mean		F	P-value
				Lower Bound	Upper Bound		
Scores of GFL related questions	Medical Doctor	51.02	19.80	45.77	56.28	12.306	0.000
	Pharmacist	70.19	25.00	65.73	74.65		
	Pharmacy Technician	59.88	30.32	47.88	71.87		
Scores of Schedule V related questions	Medical Doctor	82.78	16.98	78.27	87.28	1.170	0.312
	Pharmacist	82.19	19.42	78.72	85.65		
	Pharmacy Technician	76.43	20.83	68.19	84.67		
Total Score	Medical Doctor	66.21	15.26	62.16	70.26	5.547	0.005
	Pharmacist	75.89	20.28	72.27	79.51		
	Pharmacy Technician	67.79	23.91	58.33	77.25		

**Table 2:** One Way ANOVA Descriptions of Mean Percentage Scores vs Professions (N=207)

	Mean (%)	Std. Deviation	95% Confidence Interval for Mean		F	P-value
			Lower Bound	Upper Bound		
Not knowledgeable	16.15	17.16	0.280	32.02	65.496	0.000
Somewhat knowledgeable	62.49	14.46	58.97	66.02		
Knowledgeable	76.48	14.91	73.44	79.51		
Very knowledgeable	88.79	12.07	84.82	92.76		

**Table 3:** One Way ANOVA Descriptions of Total Mean Percentage Scores vs Overall Knowledge Rating (N=207)



**Healthcare professionals have appropriate insight on their knowledge on the medicines' entitlement system and are very interested in improving their knowledge. If adequate information is given and lack of knowledge in certain aspects is addressed, the system and society will benefit greatly.**

## DISCUSSION

The SWOT analysis identified strengths within the system, which included legislation, customer care service, reference documentation and reduction in bureaucracy. The SWOT analysis also highlighted weaknesses such as the IT system which is an out-dated and stand-alone system. A new IT system which is linked to other entities will reduce bureaucracy, improve workflow and improve the service given to patients. Moreover, with a well-designed IT system, medicines could be tracked more easily and monitoring would be carried out more efficiently.

According to the results obtained from the questionnaire, it can be concluded that healthcare professionals are more knowledgeable on the medicines entitlement system. Their knowledge regarding protocol regulated items and the availability of policy and reference documents is poor. This may be due to the fact that formularies and protocols are continuously being updated, whereas the Medicines' Entitlement System seldom changes.

The actual knowledge of participants was significantly associated with their perceived knowledge. This shows that participants have appropriate insight on their knowledge. These results are similar to the study carried out by Adiga et al in 2006.<sup>5</sup> In this study, researchers compared the actual knowledge and the perceived knowledge of internal medicine residents in Medicare Billing. Scores of participants were also significantly associated with their perceived knowledge.

## CONCLUSION

Matters related to medicines entitlement are of great interest to both healthcare professionals and patients. The strengths, weaknesses, opportunities and threats of the medicines' entitlement system can determine its success. The role of healthcare professionals is very important for the success of the system and their knowledge plays a very important role. Healthcare professionals have appropriate insight on their knowledge on the medicines' entitlement system and are very interested in improving their knowledge. If adequate information is given and lack of knowledge in certain aspects is addressed, the system and society will benefit greatly.

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# PHARMACOECONOMICS IN FORMULARY DECISION MAKING

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## ABSTRACT

**OBJECTIVES** To assess the knowledge of pharmacoeconomic (PE) information in patient groups, healthcare professionals, Government Formulary List Advisory Committee (GFLAC) and Pharmaceutical Research Based Industry Malta Association (PRIMA) members, to determine the extent to which PE information is used in formulary decision making and to define the specific challenges to adapt and establish the PE concept locally.

**METHOD** A cross sectional study was conducted to investigate local PE knowledge and trend of use. A structured questionnaire was drafted. The questionnaire was distributed electronically to GFLAC members, health care professionals, patient groups and PRIMA members. A review of international PE guidelines was carried out followed by development of another questionnaire to obtain feedback from experienced Health Technology Assessment (HTA) and PE units in European countries. This questionnaire was disseminated to European organisations after obtaining permission to use 33 European countries listed on the International Society for Pharmacoeconomics Organisation (ISPOR) and the European Network for Health Technology Assessment (EUnetHTA) mail lists.

**KEY FINDINGS** Forty out of a total of 74 electronically distributed questionnaires (response rate 54%) were returned. With regards to formulary decision making, the most influential profession was that of physicians whilst the most influential factors were drug efficacy and drug safety. The majority of participants are in favour of PE being required in formulary decision making. A total of 15 replies from 13 different European agencies were obtained. The majority of respondents agreed that Malta should adopt its own system of PE assessment. A further suggestion addressed the adaptation and tailoring of an existing national system and application of pharmacoeconomics in special cases.

**CONCLUSION** Results obtained in this study indicate that the concept of pharmacoeconomics should be required in formulary decision making and that Malta would benefit from adopting its own system of PE assessment.

**KEYWORDS** Pharmacoeconomics, Formulary Decision Making, Pharmacoeconomic Guidelines

## INTRODUCTION

Decision-makers at all levels of the health care system have been faced with increasing pressure to make more efficient use of existing health care resources.<sup>1</sup> As a result, public and private agencies worldwide have turned to evidence-based processes to improve assessment of the clinical and economic benefits of new and existing health care technologies. Although safety and efficacy are essential first considerations, Health Technology Assessments (HTAs) and economic evaluation, have become an integral component of the overall decision making process. An important subset of health economics is pharmacoeconomics which focuses solely on pharmaceuticals.<sup>2</sup> This concept is applied to guide the use of limited resources to yield maximum value to patients, healthcare payers and society.

Locally, availability of medicinal products within the Government Health Services is regulated by Legal Notice 58 of 2009 of the Medicines Act. Although the Directorate for Pharmaceutical Affairs within the Ministry for Health processes HTAs, no governmental entity is responsible for PE assessments. The aims of this study were to assess the knowledge of PE information in patient groups, healthcare professionals, GFLAC and PRIMA members, to determine the extent to which PE information is used in formulary decision making and to define the specific challenges to adapt and establish the PE concept in Malta.

## METHOD

A cross-sectional study was conducted to investigate local PE knowledge and trend of use. A structured questionnaire was drafted based on a 2010 study by Alsultan.<sup>3</sup> The questionnaire was pre-tested for face and content validity by 10 pharmacists experienced in the Government Formulary List. The questionnaire was distributed electronically to GFLAC and PRIMA members, health care professionals and patient groups. The questionnaire covered the following issues: influence of different professions in formulary decision making, potential use and helpfulness of PEs in the formulary decision making process, respondents' understanding of PE data, and barriers in the use of PEs and future expectations in formulary decision making.

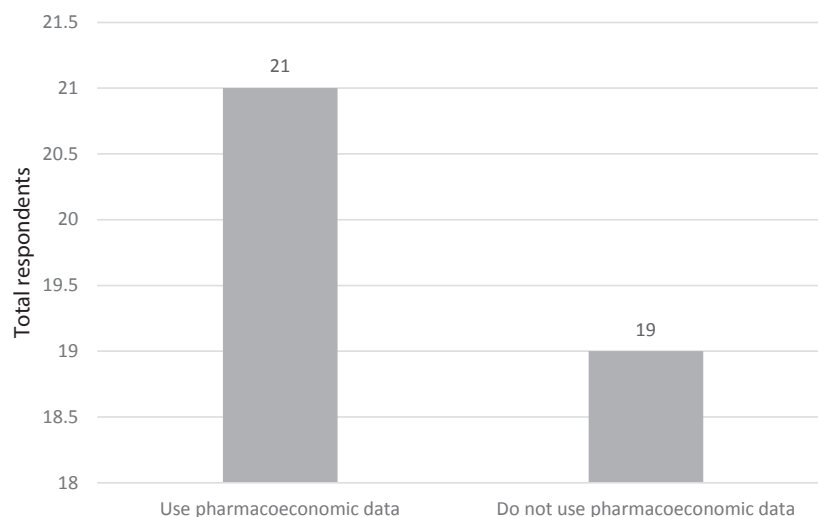
In the second part of the study a review of international PE guidelines was undertaken to determine the specific



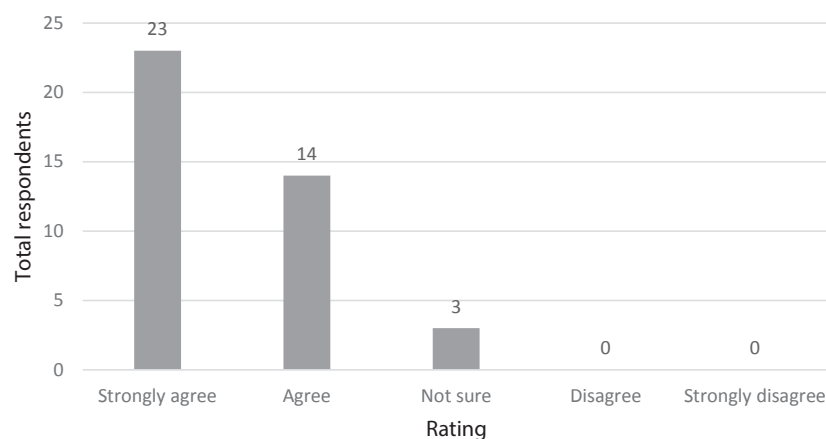
challenges to adapt and establish the pharmacoeconomic concept. Eligibility criteria for inclusion required guidelines to be European, in the English language and published from 2003 onwards. The International Society of Pharmacoeconomics and Outcome Research (ISPOR) was contacted and the investigator (SMS) was invited to use the ISPOR HTA Road Maps and PE Guidelines tools<sup>4</sup> which were relevant for the study. Feedback was obtained from experienced PE units in European countries through another questionnaire. A questionnaire based on a previous Health Working Paper by the Organisation for Economic Co-operation and Development (OECD)<sup>5</sup> was prepared. The draft questionnaire was pre-tested by 10 pharmacists for face and content validity. After obtaining permission from ISPOR and the European Network for Health Technology Assessment (EUnetHTA)<sup>6</sup>, the questionnaire was electronically disseminated to various European organisations. Topics included in the questionnaire were: the primary conceptual basis for the use of PE assessment, methods used for selecting new products and comparators for PE assessment, the accomplishments reached using PE, benefits of European co-operation for PE assessment and whether Malta would benefit from adopting its own system of PE assessment.

## RESULTS

In the first part of the study, a total of 74 questionnaires were distributed; 40 responded with the majority being females (n=21), and the age range was between 41-55 years. Most respondents were from the pharmaceutical profession (n=11). Formulary decision making, the most influential profession was found to be that of physicians (n=36) whilst drug efficacy (n=36) and drug safety (n=36) were the most influential factors. Out of these 40 respondents, 21 used pharmacoeconomic data (Figure 1). Out of these 21 respondents who use PE data, 13 rated PE data as extremely helpful or very helpful, 12 used more than one type of PE data source and 11 rated themselves as somewhat knowledgeable in the understanding of PE data. Figure 2 indicates that the majority (n=37) of participants are in favour of PE being required in formulary decision making as in other countries.



**Figure 1:** Use of Pharmacoeconomic Data (N=40)



**Figure 2:** Pharmacoeconomics in Formulary Decision Making as in other countries (N = 40)

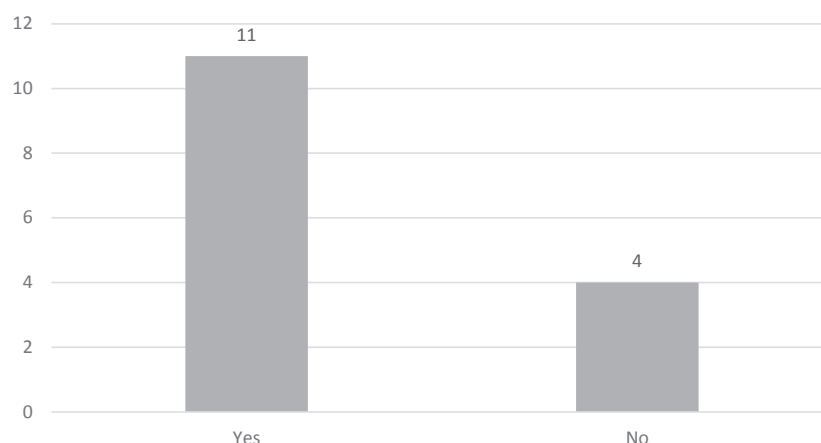
In the second part of the study, where the specific challenges to adapt and establish the PE concept were analysed, the ISPOR website has provided access to PE guidelines that are available internationally. Guidance documents are dated on the basis of publication and are categorised as: PE Recommendations, PE Guidelines, and Submission Guidelines.<sup>5</sup>

A total of 15 replies from 13 different European agencies were obtained, the majority replying on an 'own opinion' basis (n=14). Four other agencies stated that they could not participate as they do not produce PE assessments (Table 1). The primary conceptual basis for the use of PE assessment is value for money for 8 agencies, Governmental entities are

responsible for processing or conducting PE assessments in 6 agencies and pharmaceutical companies are responsible for submitting the initial PE assessment for 11 agencies. All new products are eligible in the selection of pharmaceuticals for PE assessment for 8 agencies. Overall responding agencies positively agreed that PE assessments reduced total drug expenditure (n=11), reduced unnecessary drug use (n=9), improved prescribing cost effectiveness (n=8), and sensitised drug manufacturers to the need for effective drugs (n=8).

European Agency	Country
Main Association of Austrian Social Security Institutions	Austria
Health Research for Action	Belgium
National Institute for Quality and Organisational Development in Healthcare and Medicines	Hungary
National Centre for Pharmacoeconomics	Ireland
Health Information and Quality Authority	
National Health Services	Latvia
State Health Care Accreditation Agency	Lithuania
Agency for Health Technology Assessment	Poland
Health Technology Assessment (HTA) Consulting	Poland
Scottish Medicines Consortium	Scotland
Andalusian HTA Agency	Spain
University Hospital of Geneva	Switzerland
Dutch Health Care Insurance Board/Dutch Health Care Institute (now <i>National Health Care Institute</i> )	The Netherlands

**Table 1:** Feedback from experience PE Units in Europe



**Figure 3:** Malta adopting own PE system (N = 15)

A positive attitude was observed towards European co-operation and agreement since it strengthens the role of international agencies (n=12), may create mutually agreed guidelines (n=12), may create a standard format for companies to follow when submitting assessments (n=11), supports periodic discussion meetings to discuss assessment issues (n=11), facilitates communication among national assessment groups (n=12).

Figure 3 indicates that the majority (n=11) of respondents agree that Malta should adopt its own system of PE assessment. Other feedback and suggestions include to clarify the process and disseminate information on the chosen criteria to concerned clinicians, industry and policy makers, adapt and tailor an existing national system to be more efficient and to apply PE in special cases, as Malta is a small country with limited bargaining power over pharmaceutical companies.

## DISCUSSION

The overall local results are comparable and consistent with a study conducted by Alsultan<sup>3</sup>, although in this study the target population included also representatives from patients and the pharmaceutical industry. When developing a PE approach to formulary development, the inclusion of experienced professionals, including pharmacists, who understand PE and who can analyse and convert data into useful information is considered to be critical.<sup>7</sup> In the early 1990s, Australia announced that economic analyses would be a submission requirement. Since then this policy has spread worldwide. Whilst feedback from European organisations was critical, overall results were still consistent with the 2003 OECD report<sup>4</sup>. Both the ISPOR and EUnetHTA were essential in providing a communication link with European organisations involved in PE assessments. Pressure on healthcare budgets has increased so much that harmonisation requirements for HTA across Europe has become a political priority at EU level. The European Commission is contributing millions of euro to the EUnetHTA initiative; an HTA collaboration with EU member states, amongst them Malta. This is in line with EU Cross-Border Healthcare Directive.<sup>8</sup>

## CONCLUSION

The trend appears to be that more jurisdictions, rather than fewer, are using economic analysis as part of their decision making procedures.<sup>9</sup> Economic efficiency and maximising health outcomes for a given total budget is too often sacrificed in the pursuit of cost containment. The adoption of policies that take us beyond the drug budget silo mentality should be encouraged. The findings and feedback obtained from local and European respondents in this research is clearly in favour of the adaptation of the pharmacoeconomic concept in formulary decision making in Malta. Further research is required to identify the type of guidelines and methods which would be most suitable to the local scenario.

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# COST EVALUATION OF COLLAGENASE *CLOSTRIDIUM HISTOLYTICUM* VERSUS SURGERY FOR DUPUYTREN'S CONTRACTURE

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## ABSTRACT

**OBJECTIVE** To evaluate whether collagenase injections would be a cost-effective alternative to surgery for Dupuytren's contracture in Malta.

**METHOD** An average of fifty patients per year requires surgery to correct Dupuytren's contracture in Malta. The price of collagenase injections was obtained from published pharmacoeconomic studies in Spain, United Kingdom and United States. The cost to treat multiple affected joints using collagenase injections at the different prices was compared to the costs associated with surgery in both the government and private hospital setting. A proposed price at which collagenase injections would be more cost-effective than surgery to treat two affected joints in Malta was calculated.

**KEY FINDINGS** The cost of surgery in the private hospital setting is significantly higher than that in the government hospital setting. The price of collagenase in the United States is significantly higher than in Europe. At the prices available in Europe, collagenase use in Malta would not confer significantly increased costs when treating one, two or three affected joints, both in the government and private hospital setting. Treating two affected joints rather than one affected joint does not significantly increase costs, however treating three affected joints significantly increases costs, in both hospital settings. For collagenase injections to be cost-effective in Malta, they would need to be priced at 77 Euro per vial or less.

**CONCLUSION** If all patients were to be administered the injection instead of undergoing surgery, the hospital would be able to accommodate 20 additional total knee replacements each year. With surgery costs in Malta being much less than in other European countries, there could be a possibility for Malta to attract patients from other countries. Collagenase injections would offer a less invasive treatment for the patients, and if priced at 77 Euro per vial or less, would provide a more cost-effective option to the government hospital.

**KEYWORDS** Dupuytren's contracture, collagenase, *Clostridium histolyticum*, open fasciectomy, costs

## INTRODUCTION

Dupuytren's Contracture (DC) is defined as a thickening of the fibrous tissue layer underneath the skin of the palm and fingers.<sup>1</sup> The condition is not usually painful; however over time, the collagen thickening causes contracture, leading to the affected fingers becoming permanently flexed. A diagnosis of DC is usually made when there is a positive Hueston tabletop test, where the patient is unable to fully extend the fingers and place them flat on a surface.<sup>2</sup>

The first signs of Dupuytren's Contracture are the formation of palpable collagen nodules in the palm of the hands. These collagen deposits tend to form collagen cords which usually extend longitudinally. Over time, the collagen thickens and shortens, causing the affected fingers to flex inwardly at the metacarpophalangeal joints or at the proximal interphalangeal joints. This contracture is usually irreversible.<sup>3,4</sup>

Various treatment options are available<sup>1,5</sup>; the most commonly used option is surgery, including partial or open fasciectomy.<sup>6,7</sup> In 2010, the Food and Drug Administration (FDA) followed by the European Medicines Agency in 2011, approved the first pharmacological treatment to correct Dupuytren's Contracture; an injection containing the enzyme collagenase *Clostridium histolyticum* (CCH). Collagenase injections are administered when there is a palpable cord, with a maximum of three injections given per cord at monthly intervals. Studies carried out concluded that CCH injections were a safe and effective alternative to surgery.<sup>3,8,9</sup>

It was estimated that in 2011 in England, DC related costs amounted to £41,576,141.<sup>10</sup> Economic studies were carried out in the United Kingdom (UK)<sup>11</sup>, Spain<sup>12</sup> and the United States (US).<sup>13</sup> Studies undertaken in UK and Spain concluded that CCH injections, quoting the retail price of CCH injections at the time of the study, would reduce costs associated with treatment of DC.<sup>11,12</sup> The study carried out in the US concluded that for CCH injections to be cost-effective, the price had to be one tenth of the retail price at the time of the study.<sup>13</sup>

The study carried out in Malta aimed to assess the cost-effectiveness of CCH injections at the various prices available in other countries to the cost of open fasciectomy, both in the government and private hospital settings.



## METHOD

Determination of the most common procedure to correct DC used in Malta was undertaken through discussions with all orthopaedic surgeons. Open fasciectomy was costed both in the government hospital and private hospital setting. Costs included the salary of all the healthcare professionals, cost of drugs used, utility costs and equipment costs.

The prices of CCH injections were obtained from economic studies published in the UK, Spain and the US, and converted to Euro where necessary. The cost of treating multiple affected joints was calculated for each of the prices quoted and compared to surgery in both hospital settings. An assessment was undertaken to evaluate whether the introduction of CCH injections would be more cost-effective for the different settings when compared to surgery. A proposed price for CCH injections to be cost-effective in the Maltese healthcare system was calculated.

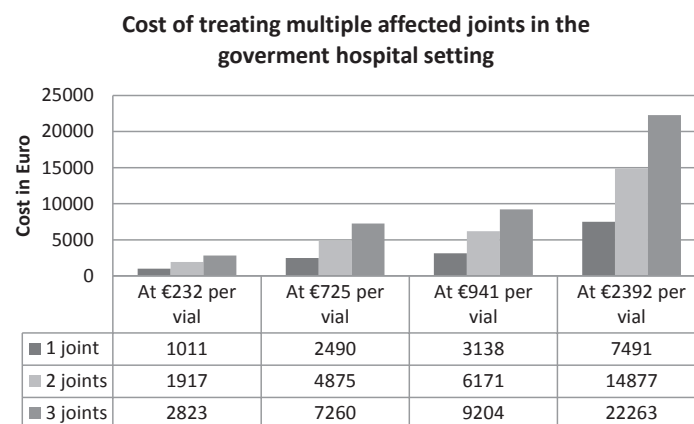
## RESULTS

Open fasciectomy at the government hospital costs €987 if performed under local anaesthesia and €1,196 if performed under general anaesthesia, including pre-operative tests,

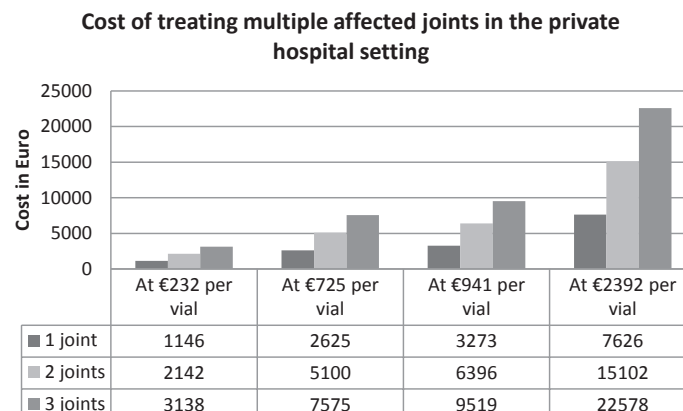
orthopaedic out-patient assessments and post-operative hand therapy sessions. The cost of surgery in a private hospital setting, including all the pre- and post-operative care is of €3,361. The cost of surgery in the private hospital setting is significantly higher than in the government hospital ( $p = 0.029$ ).

The last known price of one vial of CCH injection was €725 in Spain, £780 in the UK and \$3,250 (actual price) and \$315 (proposed maximum price) in the US. These values were converted to Euro to enable comparison: €941 for the UK, €2392 actual price in the US and €232 proposed price in the US (as per exchange rate of 5 January 2014). The cost of CCH injections in the US is significantly higher than in Europe ( $p = 0.033$ ). The proposed price for the US would significantly reduce the difference ( $p = 0.113$ ).

Figures 1 and 2 show the cost of treating multiple affected joints with CCH injections at the different prices available, for the government hospital setting and for the private hospital setting respectively. At the prices available in the EU, the cost of using CCH injections was not significantly higher than surgery in both the government and private hospital setting when treating one ( $p = 0.112, 0.424$ ), two ( $p = 0.09, 0.169$ ) or three ( $p = 0.085, 0.118$ ) affected joints.



**Figure 1:** Cost of treating multiple affected joints in the government hospital setting at CCH prices available.



**Figure 2:** Cost of treating multiple affected joints in the private hospital setting at CCH prices available

Breakdown of costs	Government hospital		
Number of joints affected and number of injections needed	1 joint, 3 injections	2 joints, 6 injections	3 joints, 9 injections
Cost of injections	€231	€462	€693
Number of out-patient visits needed (at €35 each)	9	15	21
Cost of out-patient visits	€315	€525	€735
<b>Total</b>	<b>€546</b>	<b>€987</b>	<b>€1,428</b>

**Table 1:** Cost of treating one, two or three affected joints with collagenase injections at the proposed price (€77 per vial) for the Maltese market

The cost increase to treat one additional joint at the prices available in Europe does not significantly increase the hospital's expense in both the government and private hospital setting ( $p = 0.139, 0.129$ ), both when comparing two joints over one, and three joints over two. The cost to treat two additional joints results in significantly higher costs ( $p = 0.024, 0.022$ ).

The proposed price for CCH injections in Malta was calculated to be cost-effective when compared to surgery and aftercare to treat two affected fingers. With the majority of patients undergoing treatment at the government hospital, the surgical cost of €987 was taken as the maximum total cost. When taking into consideration the cost of required out-patient visits, the proposed price was €77 per vial or less (Table 1).

## DISCUSSION

When comparing the cost of open fasciectomy in the government hospital setting to the cost of the same surgery in the private hospital setting, this difference in cost was proven to be statistically significant. Reasons for this are numerous, with the most important one being that the government hospital is fully subsidised by the government. In a private hospital setting, the hospital is dependent on the income it obtains from patients using its services to stay in business, pay bills, buy and maintain new equipment and at the same time, still offer a high standard of care. Medicines are purchased at the full price, not on tender, and no expense is subsidised by government funds.

The cost of treating one, two and three affected joints with CCH at European prices in the government hospital setting compared to the cost of open fasciectomy, showed that there was no significant increase in hospital costs. However, this could be a paradox, mainly due to the large internal variance of collagenase prices. This is especially important

when one considers that treating three affected joints with collagenase costs €7,260 in Spain and €9,204 in UK, as compared to €987 for open fasciectomy using local nerve block with sedation. The fact that the results do not show a significant difference in costs could be due to the large variance in the data. If EU prices were more homogenous, statistical results could show a significant increase in costs.

In the private hospital setting, treating one, two and three affected joints also gave no significant increase in costs when compared to open fasciectomy. However, treating three affected joints with collagenase injections costs nearly three times as much as open fasciectomy. The large variance in cost could also be the reason for this result. This highlights the need to have more homogenous prices, not just between EU member states, but also with other countries.

Apart from economic considerations, using CCH injections to replace surgery could have other benefits in the Maltese healthcare system. The government hospital, falling under the responsibility of the Health Ministry and the Finance Ministry for budgetary approval, has a responsibility to make the best use out of the limited resources available.

The government is also under pressure from the public to reduce the waiting list for surgeries. An article published in The Sunday Times of Malta on 27th October 2013 listed the Orthopaedics Department as the one with the most patients waiting to be given a date for their surgery. Most of these patients are waiting for total hip or knee replacements. Taking this into consideration, if all patients needing open fasciectomy for Dupuytren's Contracture were switched over to CCH injections, an additional twenty total knee replacements could be performed every year.



## Apart from economic considerations, using *Clostridium histolyticum* injections to replace surgery could have other benefits in the Maltese healthcare system.

### CONCLUSION

Collagenase *Clostridium histolyticum* injections, at the prices last available on the market, would not be a cost-effective option for treating Dupuytren's Contracture in the government hospital. Open fasciectomy in the state hospital costs much less than in the private sector mainly due to the running costs.

In the private sector, CCH injections are more cost-effective than open fasciectomy when only one finger is affected. When multiple fingers are affected, open fasciectomy remains the least expensive option. At the prices available in Europe, using CCH injections in the private sector would always be less expensive than surgery if only one finger is affected. With open fasciectomy and aftercare costing €3,361 per patient, CCH injections would result in savings ranging from €88 (if CCH is priced €941 at per vial) up to €736 (if CCH is priced at €725 per vial). When two or more fingers are affected, the results are reversed. With the cost of treating two fingers with CCH injections amounting to a minimum of €5,100 (when CCH injections are priced at €725 per vial), injections would be more expensive than open fasciectomy by a minimum of €1,739.

With the majority of patients having one or two fingers affected, CCH injections need to be less expensive than surgery to be cost-effective, and should ideally cost €77 or less per vial, to be at an equal cost to surgery in the government hospital.

If all patients treated at the government hospital for Dupuytren's Contracture are switched to collagenase *Clostridium histolyticum* injections, the hospital would be increasing its expenses, but at the same time it would free operating theatre hours that could be used for other procedures, thus reducing patients' waiting lists.

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### Disclaimer:

During the initial stages of the study, the corresponding author was an employee of Pfizer. At the time, the marketing authorisation for collagenase injections had already been sold by Pfizer to Auxilium Pharmaceuticals.

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ABSTRACT

# QUALITY RISK MANAGEMENT IN PARTIAL MANUFACTURING OPERATION

Richard Despott

## OBJECTIVE

To identify key quality issues concerning pharmaceutical manufacturing activities and develop standards for a Quality Management System in line with legal requirements and EU Guidelines.

## METHOD

Standards for a Quality Management System (QMS) were developed, based upon underlying principles of regulatory requirements combined with a risk management approach.

A Master set of Standard Operating Procedures (SOPs) were identified based on literature review. A standard was then developed for each of the procedures, directly from the legal text of the EU Good Distribution Practice guidelines and annexed documents, thereby ensuring that the principles underlining the relative regulatory requirements were included.

The core standards of the QMS were derived by applying the principles to operational practices in conjunction with a risk assessment of existing operations.

## KEY FINDINGS

A master set of 32 SOPs was compiled and their respective standards were developed to produce a QMS model that would regulate and control all aspects required for licensing of partial manufacture operations and management of major risks involved in related procedures.

## CONCLUSION

Effective SOPs must be based on specific operational conditions in order to ensure compliance with regulatory requirements and the consistent quality of manufacturing processes. However the core system of procedures and related standards identified by the research provide a basis for development of a pharmaceutical quality management system that can be applied across a variety of different contexts.

## KEYWORDS

Quality Management System, Standard Operating Procedure, Operational Standards



## GUEST CONTRIBUTION

# A HISTORICAL PERSPECTIVE ON PHARMACOPOEIA

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Drugs were doubtless developed when man's life started on Earth. All beings, and humans too have always sought ways to overcome their ailments and diseases. Humans have tried to improve their living conditions and lengthen their life using various objects from the wildlife that once, intuitively and empirically, improved their health or at least palliated their ailments. Perhaps the origin of the pharmacopoeias, could be the set of useful remedies for curing human illnesses that have come through Egyptian, Mesopotamian, Chinese, Indian, Greek, Roman, Islamic and Christian cultures and that throughout history have been improving and adapting.

The same fact happened in Mexico and Peru. Before Islam arrived, there was no professional division between physicians and pharmacists. With more or less technical and scientific training, the same individual practised both activities. In the ninth century in Baghdad, the separation of tasks was initiated: physicians were responsible for diagnosis and prognosis of diseases and pharmacists were responsible for the preparation of medicines. Later, over time, the classic medical order given to the pharmacist would be expressed in recipes or prescriptions: 'Fiat secundum artem' or 'Dp/DPS' (Dispense). Once this separation occurred, the first books aimed at physicians and pharmacists appeared in order to establish their duties. These books were intended to expedite the prescriptive functions to physicians and the preparation of remedies to pharmacists, so that the medication given to patients of a certain territory was similar. Thus, we might consider the term pharmacopoeia as 'the book of drugs, the book of health'.

During the European Christian Middle Ages, the authentic legal separation between Medicine and Pharmacy took place by prohibiting the exercise of both professions at the same time, but it was not a divorce. This circumstance happened during the Reign of Federico II, King of Sicily, in 1240, considering this fact, therefore, as the 'Magna Carta of

Pharmacy'. The above mentioned separation began in Italy, continued in France and Spain, and then it was extended throughout the rest of Europe. Since then, as required by law and generally accepted, the pharmacopoeias have arisen in their modern conception. Consequently, these books are intended to specify the preparation of medicines for an essential and mandatory use for physicians who prescribe and pharmacists who prepare the medicines within a certain geopolitical unit. Pharmacopoeias are, therefore, official books, primarily intended for physicians and pharmacists; for this reason, they are part of the history of science and culture as they are related to daily life, illness and the humans' desires to prevent diseases and preserve their health. In consequence, it could be argued that pharmacopoeias are an essential part of the history of humanity, a text whose mission is to establish the characteristics of drugs and has legal force or has been accepted in order to harmonise the professional practice in a given territory. The first official pharmacopoeia was the Ricettario Fiorentino, whose full name was 'Nuovo receptario composto dal famosissimo Chollegio degli eximii Dottori della Arte et Medicina della ínclita ciptá di Firenze' printed in Florence in 1498, whose mission was to try to eliminate the large differences in this city, according to the different ways of preparing medicines. In that 'ricettario' three parts can be distinguished: one aimed at identifying samples, other for compounds and the last one at establishing certain forms of complicated processing; this pharmacopoeia also included a section for weights, measures and synonyms. It was written by physicians, and allowed to facilitate their relationships with pharmacists. Physicians prescribed the medication they wanted for their patients and pharmacists perfectly knew how to prepare it. In conclusion, this book simplified everything. Thus, the same medicine would receive the same name for being prepared in a pre-established way.

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## The knowledge of the importance of analytical methods presented in the lifecycle of a drug is as necessary an approach as knowledge about the different stages of drug development.

Then appeared the Catalan Concordias: Concordia Apothecariurum Barchinonensium, published in Barcelona in 1511; Concordia Pharmacopoliarum Barchinonensium, 1535; Concordias of Saragossa, Concordia Aromatariorum civitatis Cesarauguste, 1546 and 1553, Dispensatorium Pharmacopolarum, 1546, and then the one of Mantua (1559), Cologne (1565), Vienna (1570), Montpellier (1579), Rome (1583), Ferrara (1595).

In the Iberian Peninsula, the first pharmacopoeias appeared in the Kingdom of Aragon, territory where trade associations were stronger, the exercise of pharmacists was better established and these professionals were considered as people of influence. In Valencia the pharmacopoeias *Officina Medicamentorum* were published in 1601 and 1693, and after them, the first Spanish Pharmacopoeia to be enforced for the whole of Spain, the *Pharmacopoeia matritensis*, was published in Madrid in 1739.

The analysis and control of drugs is an area of knowledge of prime importance both in the development of new drugs, and in the control of the existing ones. The need to ensure the effectiveness, safety and quality of medicines requires verification, monitoring and control systems, increasingly becoming sophisticated and also subject to a rigorous and varying regulations, according to the scientific advances. Hilarión, a famous pharmacist, already said in the Madrid noted zarzuela called 'La Verbena de la Paloma' by Tomás Bretón, that sciences advanced in an outrageous way.

The knowledge of the importance of analytical methods presented in the lifecycle of a drug is as necessary an approach as knowledge about the different stages of drug development. In this sense, analytical techniques play a crucial role in all stages of a drug, in other words, these stages include: the research, the development of a new compound, the study of the suitable pharmaceutical form and the production and control as well as the knowledge of the state of conservation.

One of the most important uses of instrumental techniques in Pharmacy is undoubtedly the qualitative and quantitative determination of compounds which act as active ingredients or excipients of medicines. There are numerous methods that are regularly used for this purpose; being necessary to know the possibilities and limitations of each of them in order to select the most suitable method for the analysis that must be performed. It is sometimes possible to combine two or more techniques to solve specific problems.

The term ICH strongly arises (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). This Conference was originated in Europe, Japan and the United States, as a result of various events occurring in the decades prior to 1970. ICH comes together in the 1980s, in the European Union, its birth being regarded in Brussels in April 1990. The objectives of ICH are mainly to regulate the various technical and scientific methods used in Europe, Japan and USA, as regards medicines.



## GUEST CONTRIBUTION

# THE RELATIONSHIP BETWEEN BIOLOGICALS AND INNOVATION

Daan J. Crommelin

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## THE PRICE OF MEDICATION: NOVEL BIOLOGICALS

There are no two European countries with the same – or even similar – health care systems. But they share one common denominator: in all European countries the costs for health care keep on rising faster than their GDP. The growing number of elderly people and the related extra claim to the system can only partly explain this cost increase. There are other drivers as well. Although the increasing use of generic drugs tends to reduce the cost of medicines, there is an upward pressure through the category of novel medicines, in particular biologicals: medicinal product made through recombinant DNA technology. In the list of 10 best-selling drugs (total sales 75 billion US\$ in 2013), 7 out of 10 are biologicals (Table 1). All 7 sell between 5 and 10 billion US \$ per annum. These biologicals are used to treat serious, often life-threatening diseases, such as cancer and diabetes. And the price for the annualised cost of treatment per patient can be as high 100,000 Euros or even higher (Table 2).

1. <b>Humira</b>	6. <b>Rituxan/MabThera</b>
2. <b>Enbrel</b>	7. <b>Avastin</b>
3. <b>Remicade</b>	8. <b>Herceptin</b>
4. Advair/Seretide	9. Crestor
5. <b>Lantus</b>	10. Abilify

Biologicals are in **bold**

**Table 1:** Number 1-10 blockbusters in 2013, From FiercePharma, March 25, 2014

Product	Indication	Annualised cost per patient in US	Biomarker	Population testing positive for biomarker (%)	Projected sales (2012-2018)
<b>Erbix</b>	Colorectal, head and neck cancer	\$84,000	EGFR+ KRAS-wt	37.5	\$13.42 billion
<b>Herceptin + Perjeta</b>	Breast cancer	\$124,800	HER-2+	25	\$49.96 billion
<b>Tarceva</b>	Non-small cell lung cancer	\$52,800	EGFR+	10-15	\$10.8 billion
<b>Xalkori</b>	Non-small cell lung cancer	\$115,200	ALK+	4-7	\$4.76 billion
<b>Zelboraf</b>	Melanoma	\$112,800	BRAF+	13.5	\$4.25 billion

Sources: EvaluatePharma and ThePinkSheet

Note: Projected sales are cumulative and global.  
www.pwc.com/pharma2020

**Table 2:** Targeted medicines with companion diagnostics generate high revenues because they work so well for specific patient segments

Product	Price (US\$)	Price/g (US\$)	Manufacturing cost * (US\$/g)	Cost/price difference
Avastin (bevacizumab)	687.5/100mg	6875	188	2.7%
Enbrel (etanercept)	243/25mg	9706	428	4.4%
Humira (adalizumab)	1816/40mg	45400	308	0.7%
Rituxan (rituximab)	675/100mg	6751	188	2.8%
Herceptin (trastuzumab)	3331/440mg	7570	126	1.7%
Erbix (cetuximab)	600/100mg	6000	188	3.1%
Soliris (eculizumab)	5122/300mg	17073	135	0.8%
Remicade (infliximab)	784/100mg	7839	188	2.4%
<b>Average</b>		<b>12877</b>	<b>231</b>	<b>2.3%</b>

\*Assuming 2g/L yield

International Journal of Medical and Pharmaceutical Sciences (IJMPS) Vol 1 issue 7, 2012 taken from Gal 2014

**Table 3:** Difference between cost of manufacture and price

To explain the high prices of biologicals, two arguments are being used: I) these products are very costly to produce, because of the complex manufacturing process including downstream processing, and /or II) the cost for innovative drug product development is high: 4.2 billion+ euros (period 2006-2012) for a successful product including the money to be recouped for the many failed drug products in the pipeline ('attrition') (PWC, 2012). And, somebody has to pay the bill. In the following I will demonstrate that the manufacturing costs argument is incorrect and that indeed 'big pharma' is –for now– still profitable because of these highly successful biologicals. But there is more to it.

## THE HIGH COST MANUFACTURING MYTH

Admittedly, the production process of biologicals is complex. But, experience with generic/follow-on versions of biologicals (the term 'biosimilar' should not be used as it is restricted to EMA/FDA approved biological drug products) in countries such as India, China and Thailand teaches us that indeed the price can be reduced substantially, although there are questions about the quality of these 'bioquestionables' (Hakim et al., 2014). E.g.,

a follow-on version of Humira® will be sold in India at 20% of the originator's price (1000 \$ per injection)(Ail, 2014). Undela (from Gal 2014), published a list (Table 3) where the difference between costs of manufacturing and (whole) sale(s) price is listed for a number of biological blockbusters. On an average, manufacturing costs make up 2.3% of the price. Therefore, the argument that these biologicals are expensive due to the manufacturing process is not convincing at all (cf. Undela, 2014; Gal 2014). In conclusion, manufacturing costs cannot be the reason for the high annual costs listed in Table 2.

The high margins are not specific for novel biological medicines. For some novel small molecule medicines similar situations are encountered. The new anti-hepatitis C medicine Sofosbuvir is sold (wholesale price) for US\$ 84,000 for a 12 weeks of treatment course used for genotypes 1 and 2 (about US\$ 1,000 per pill) and US\$ 168,000 for the 24 weeks course used for genotype 3. But the costs for manufacturing are close to 150 US\$/course (Wikipedia). Interestingly, the innovator company (Gilead) will sell the drug for much lower prices in developing countries, e.g. for 300 US\$ per course in India (<http://en.wikipedia.org/wiki/Sofosbuvir>).



## ARE THE BIOLOGICAL BLOCKBUSTERS SAVING 'BIG PHARMA' AND IS THE CURRENT SYSTEM SUSTAINABLE?

The second argument to explain the exceptionally high prices (Table 2) is the sustainability of the current 'big pharma' business model. Many analyses have been published that investigated the costs for the development of new medicines. The PWC report uses a simple calculation (PWC 2012). Between 2002 and 2011 pharma industry spent 1.1 trillion US\$ on R&D for the 308 NME (new molecular entities) introduced as medicines in that period. And voila, the average cost per NME over that 10 year time frame is 3.6 billion US\$. The questions can be raised: 1) How to recoup these enormous amounts of money and in particular recoup from whom? And 2) Why is drug development such an expensive activity? Is the present business model sustainable?

The research and development investment has to be recouped before the patent expires or within the period of 'data exclusivity and market protection' (cf. EMA 2013). At present, the main source of payment for innovative medicines are the Western world health care systems, in particular in the USA where the prices as listed in Table 2 are being paid.

But, there is a growing concern about the sustainability of this business model with the Western world taking most of the costs of the innovation. Many wonder whether the innovation cost burden should be spread more evenly around the world and include emerging economies.

The second question was (re 2): Why is drug development such an expensive activity? Is the present paradigm sustainable? To answer that question, excellent analyses and recommendations have been published. The PWC 2020 report and the article by Munos, 2009, are mainly dealing with the industry perspective. Eichler et al. 2008 and 2013, are discussing the regulatory position regarding conditional and accelerated approval, the 'risk of risk avoidance' (type II errors) and patient advocacy. What is the big challenge now? All stakeholders in the drug development process (industry, academia, regulatory bodies, patient organizations and political parties) should sit together, critically (re)consider their positions and hammer out a new –global– paradigm for drug development. This could include, e.g. spending less money in clinical phases, in particular phase II/III. That means reduce attrition in a late phase of the development process ('kill' candidate medicines in an early stage) and further strengthen the science base for the regulatory system, e.g. avoid the 'precautionary principle' mind set and continue to work on new, globally harmonized, approval procedures understood and supported by all stakeholders throughout the whole world. These measures should lead to an efficient, economically sustainable and fair system to bring highly needed NMEs to the patient. A formidable task, but a lot of preparatory work has already been done and there is no time to lose!

We need innovation in the pharmaceutical world. Just read the challenges and desired/required new medication listed in the WHO Report on Priority Medicines 2013 (Kaplan et al., 2013). And we, the stakeholders, all have to contribute ideas and commit to make the new, sustainable system work.

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# PHARMACEUTICAL RESEARCH AT THE DEPARTMENT OF PHARMACY

The following are examples of research projects carried out by Ph.D. candidates  
who are Research Officers at the Department of Pharmacy

## INNOVATIVE TOOLS TO INVESTIGATE RISK IN PHARMACEUTICAL PROCESSES

*Maresca Attard Pizzuto*

Risk is part of daily language and is used in a variety of contexts and scenarios. One might talk about 'risk' as the probability of an incident happening or not happening, about success or failure. Organisations would never evolve without taking risks which can have overwhelming consequences with respect to economic performance and professional status. Risk management, being a preventive and predictive tool, is increasingly becoming a fundamental part of processes for the pharmaceutical and biopharmaceutical sectors as it combines aspects of economics, maturation of quality management systems, standards, global harmonisation, new strategic models and allied responsibility. The Department of Pharmacy at the University of Malta is actively participating in 'Risk' projects by dedicating a research group on 'Risk'. Some of the risk research questions being studied by this group are issues concerning patients self-administering medication, dispensing over-the-counter (OTC) and products being OTC rather than pharmacist recommended and risks involved in the partial manufacturing of pharmaceuticals. Another case scenario being studied includes pharmacist prescribing as compared to present prescribing practices by medical doctors. Such studies will help pharmacists identify risk scenarios in different pharmaceutical processes, rank and analyse the different risks, devise risk management plans and implement risk mitigation strategies to improve outcomes in various pharmaceutical settings.

## NEW PATHWAYS FOR DEVELOPMENT OF SYNTHETIC STEROIDS

*Nicolette Sammut Bartolo*

The increased awareness towards the need to safeguard the environment was also reflected in the pharmaceutical industry whereby in 1998 the concept of Green Chemistry and its twelve principles were introduced by Paul Anastas and John Warner. During the synthesis of active pharmaceutical ingredients various reagents, catalysts and solvents are used which may have an impact on the environment. The research which is currently being undertaken at the Department of Pharmacy aims to develop a pathway for the synthesis of a steroid which has a lower impact on the environment using the Green Chemistry principles. Methods which make a pathway greener include the use of greener solvents and catalysts, decrease in the amount of solvent and reagents and catalysts used and decrease in the energy required to carry out the reaction. Factors which affect the synthesis of steroids are looked into taking in consideration the yield.

## DISTRIBUTION OF ANTI-INFECTIVE AGENTS IN THE PERIPHERIES

*Janis Vella*

Malta ranks among the European countries with the highest prevalence of diabetes. Peripheral arterial disease (PAD) is a chronic and debilitating illness which results from functional and anatomical complications. In a diabetic patient suffering from a lower extremity infection, the presence of significant PAD impairs delivery of the required dose of antibiotics to the infected tissues. A standard antibiotic dosage regimen may lead to sub-inhibitory concentrations at the target site. This decreases the effectiveness of antimicrobial therapy. In light of this, innovative High Performance Liquid Chromatography methods to quantify the concentration of antibiotics in human plasma and tissue were developed. These methods are subsequently being used to quantify antibiotics in the peripheries of patients with PAD to establish if the dosage regimen given is sufficient to eradicate the infection at the target site. Other significant parameters affecting lower limb antibacterial drug tissue concentrations are being looked into. A pharmacokinetic equation to predict the concentration of antibiotics in patients with PAD is being developed. This can help in more adequate dosing in such a group of patients with less undesirable effects and better treatment outcomes, avoiding unwanted complications and achieving higher levels of therapeutic success in the process.

## PHARMACOGENETIC IMPLICATIONS IN CLOPIDOGREL THERAPY: A PHARMACIST- LED MANAGEMENT APPROACH

*Francesca Wirth*

Clopidogrel is a pro-drug requiring activation by the cytochrome (CYP) 2C19 enzyme to exert its antiplatelet effect. Patients who have reduced functioning of this enzyme, due to presence of one or two loss-of-function (\*2) alleles, cannot effectively convert clopidogrel to its active form and have a 42% higher risk of major adverse cardiac events due to decreased clopidogrel effectiveness. Guidelines recommend that carriers of the \*2 allele should be switched to an alternative to clopidogrel, such as prasugrel, provided there is no contra-indication. The current scenario in Malta is that clopidogrel is given to all patients with coronary artery disease who have undergone a percutaneous coronary intervention (PCI), or have been admitted to hospital with an acute coronary syndrome, without screening for clopidogrel resistance. Alternative antiplatelet agents to clopidogrel are not available on the local Government Formulary List. This research involves pharmacist-led determination of the presence of the CYP2C19\*2 allele in patients on clopidogrel therapy following a PCI. Having this genotype information, the clinical pharmacist will be able to support cardiologists in the personalisation of antiplatelet therapy to try to limit occurrence of stent thrombosis, re-infarction and other cardiovascular events in these patients. Pharmacoeconomic analysis of routine CYP2C19\*2 genotyping is undertaken and recommendations for review of national pharmaceutical policies for antiplatelet therapy are put forward.



# MALTA PHARMACEUTICAL STUDENTS HEALTH CAMPAIGN TO COMMEMORATE WORLD PNEUMONIA DAY



Matthew Zarb, MPSA Publications Officer



MPSA Executive members 2014-2015

MPSA has over the past year organised a series of health campaigns to raise awareness. One of these campaigns was held last November to commemorate World Pneumonia Day.

Pneumonia is an inflammatory condition of the lungs affecting the lower airways, or more specifically the alveoli (air sacs). The causative agents of this inflammation are usually bacteria or viruses.

Bacteria are the most implicated in cases of community-acquired pneumonia, in which *Streptococcus pneumoniae* and *Haemophilus influenzae* stand out as the leading pathogens in 50% and 20% of cases respectively. Pneumonia presents itself through many symptoms, the most common being: fever, fatigue, a productive cough, shaking chills, dyspnoea, tachypnoea) and sharp chest pain on deep inhalation. It is important to point out that the cough itself may be absent in young children (usually less than 2 months old).

Severe cases of pneumonia may be accompanied by cyanosis in the core area as well as the lips and tongue. This is caused by insufficient oxygenation of these areas, which is due to the build-up of fluid in the alveoli, resulting in the gas exchange process being hindered.

Smoking and chronic obstructive pulmonary disease are two major predisposing factors. Uncontrolled diabetes as well as excess alcohol intake may also increase the likelihood of

infection and risk of developing pneumonia. Children and the elderly are the most vulnerable age groups susceptible to infection.

There are currently two types of vaccines available for prevention. The first is indicated and usually reserved for the elderly (more than 65 years of age), and contains a mixture of different polysaccharide capsular serotypes (unbound to protein) derived from capsulated bacteria themselves. A single dose is given in this case. The second vaccine available is indicated for children and contains a mixture of different polysaccharide capsular serotypes, which are conjugated with carrier proteins derived from *Corynebacterium diphtheriae*. This is given at 2, 4, 6 and 15 months of age.

Recent studies have seen the Centres for Disease Control and Prevention (CDC) recommend the latter vaccine for the elderly too.



Banner used to commemorate World Pneumonia Day 2014

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# 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.

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

## KEYWORDS

Three to five keywords should be provided.

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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.

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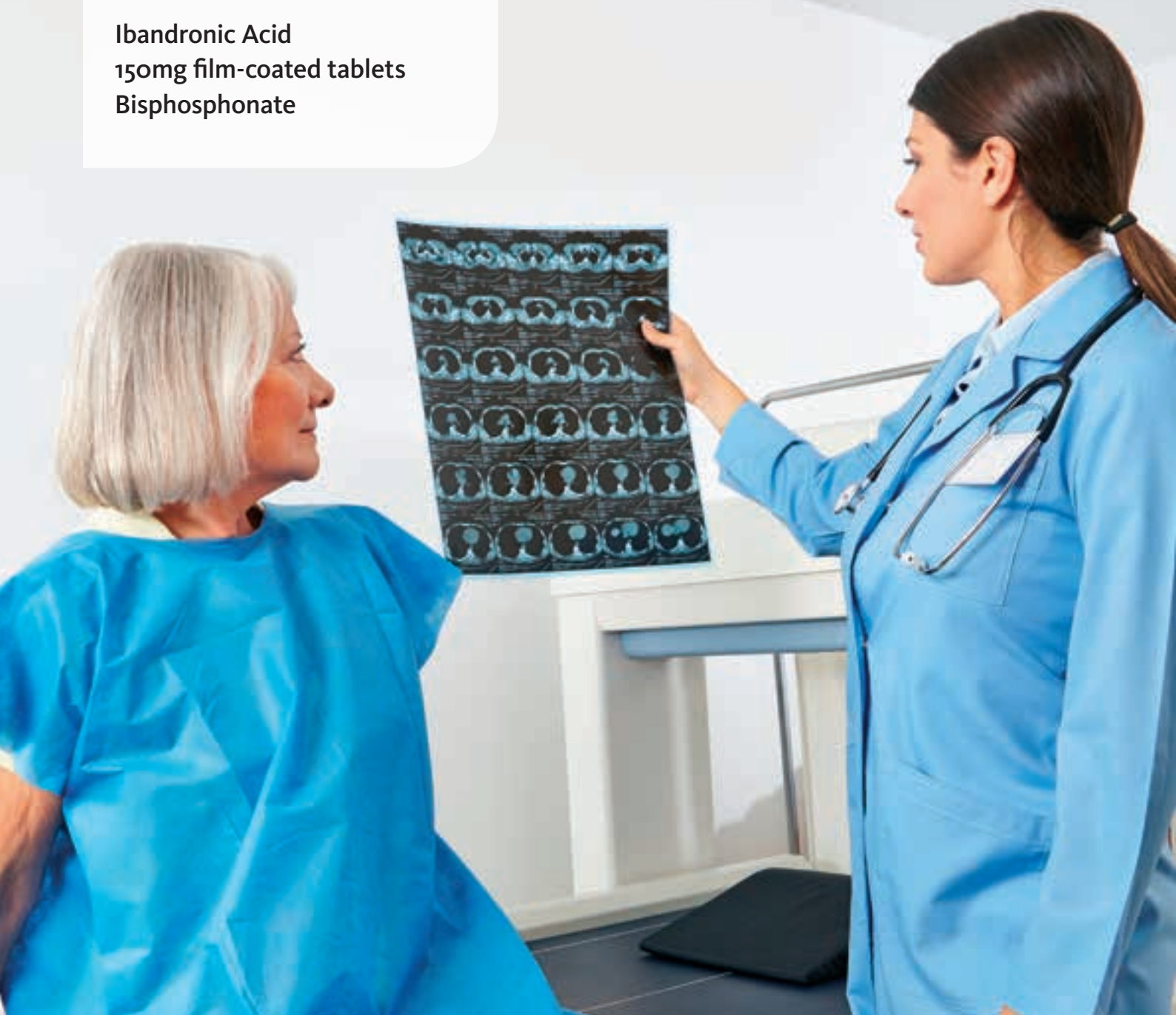
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