Medicine Shortages

A thesis submitted in partial fulfilment of the requirements of the Degree of Doctorate in Pharmacy

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To my dearest family and friends. I would have never had made it to this point without your constant support and love

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Abstract

Medicine shortages are caused when disruptions in the supply chain affect patient accessibility to medicines. Clinical, economical and humanistic impacts on the patients, healthcare professionals and the national health systems result from lack of accessibility to medicines. The aims of this research were to (i) study the perception of family doctors, pharmacists and patients when facing medicine shortages in the community setting (ii) evaluate the rationale of exemption from registration due to a justified public health need in accordance with Article 20 of the Medicines Act Chapter 458 of the Laws of Malta, (iii) develop criteria to classify and measure risk associated with evaluating an application for an Article 20 exemption.

The methodology was divided into three studies: 1. Development and validation of three questionnaires intended for family doctors, patients and pharmacists to study their experience with medicine shortages in a community pharmacy setting. 2. Formulation of a database to retrospectively analyse and examine trends in Article 20 applications from October 2020 to April 2022. 3. Establishment of a critical therapeutic class list through focus group discussion and development of a risk matrix tool to optimise processing of Article 20 exemption applications.

The questionnaire was answered by 50 pharmacists, 20 family doctors and 200 patients. All the pharmacists (N=50), 18 family doctors and 113 patients experienced medicine shortages in the last 5 years from community pharmacy setting. When patients were asked if medicine shortages were solved to their satisfaction, 49 patients stated that the alternative medicine recommended was not effective, 29 patients stated that no alternative was available, 16 patients stated that alternative medicine caused unwanted side effects and 10 patients stated that medicine alternative was higher in price. Family doctors and

pharmacists were asked about impact medicine shortages had on patient care. Twenty pharmacists and 11 doctors stated that it caused distress and inconvenience, 12 doctors and 8 pharmacists stated that medicine shortage lead to sub-optimal treatment, 11 doctors and 9 pharmacists stated increase in expense to patient, 9 doctors and 7 pharmacists stated cancellation of care, 8 doctors and 15 pharmacists stated delays in treatment and 6 doctors and 12 pharmacists stated medication error. Descriptive statistics of retrospective analysis of Article 20 exemptions was carried out with 636 applications being approved and 25 applications rejected. The most prominent reason for requesting an Article 20 exemption (247 applications) was interim supply until the National Health System finalizes the tender. Through focus group discussion, risk matrix categories for risk severity and risk probability were identified. The risk critical numbers were identified and categorized into ranges. For a low risk to patient the range was identified to be 1-4, for medium risk the range was identified to be 5-10, for high risk the range was identified as 12-25.

Six hundred and thirty-six medicines were prevented from shortage through the granting of an Article 20 exemption to ensure continuous access of medicines to patients. A risk prioritization tool was found useful to limit the impact of medicine shortages on the patient. The study showed that evaluating the rationale and generating trends observed from Article 20 exemptions granted determines which medicines most likely be in shortage prospectively whereby mitigation of such shortages can be carried out nationally.

Keywords

Medicine Shortages – Risk - Perception –Access – Article 20 exemption – Patient Impact

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Glossary

Article 20

Article 20 is an emergency exemption in accordance with the Medicines Act Chapter 458 of the Laws of Malta, which is granted by the Licensing Authority, under guidance from the Malta Medicines Authority for a medicinal product not currently holding a marketing authorization under strict exceptional cases. The exemption is subject to pre-determined conditions and requires Medicines Authority to review each Article 20 application on a case-by-case basis.

Reference: Article 20 of Chapter 458 of the Laws of Malta, Available from URL: https://legislation.mt/eli/cap/458/eng/pdf

Brexit

The withdrawal of the United Kingdom from the European Union in 2020.

Reference: Arnorsson A, Zoega G. On the causes of Brexit. European Journal of Political Economy. 2018;55:301-323.

Critical Medicine (EMA)

The European Medicines Agency (EMA) states that a definition of a critical product depends on two factors: therapeutic use and availability.

Reference: European Medicines Agency (EMA) Criteria for classification of critical medicinal products for human and veterinary use. EMA/24304/2016. Available fromURL:https://www.ema.europa.eu/en/documents/other/criteria-classification-critical-medicinal-products_en.pdf

EAHP Medicines Shortages Report

The European Association of Hospital Pharmacists (EAHP) conducts a medicine shortage survey with hospital pharmacists every few years with several EU countries. In 2019, the survey was extended to doctors, patients, nurses and other healthcare professionals. First published in 2012, the latest medicine shortage survey was carried out between November 2019 and January 2020.

Reference: European Association of Hospital Pharmacists. (EAHP) 2019 EAHP Medicines Shortage Report. 2020. Available from URL: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf

Essential medicine list (WHO)

World Health Organization medicine list contains the selection and use of medicines the organization deems as essential for every country. The list is updated every two years by the Expert Committee of Selection and Use of Essential Medicines. First published in 1977, the latest essential medicine list is the 22nd essential medicine list updated in September 2021)

Reference: World Health Organization (WHO). WHO Model Lists of Essential Medicines. Available from URL: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

POYC

Pharmacy of Your Choice is a scheme that provides patients with medicines and medical devices for free by the National Health System through the patient's preferred pharmacy.

Reference: Pharmacy Of Your Choice Scheme, Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/Poyc-scheme.aspx).

List of Abbreviations

AESGP	Association of the European Self-Medication Industry
ATC	Anatomical Therapeutic Chemical
EAHP	European Association of European Hospital Pharmacists
EAEPC	The European Association of Euro-Pharmaceutical Companies
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIPG	European Industrial Pharmacists Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
FIP	International Pharmaceutical Federation
GIRP	European Healthcare Distribution Association
HMA	Heads of Medicines Agency
HTAs	Health Technological Assessments
MAH	Marketing Authorisation Holder
MMA	Malta Medicines Authority
MIAU	Medicines Intelligence and Access Unit
SPOC	Single Point Of Care
POYC	Pharmacy of Your Choice
WHO	World Health Organization

Chapter One

Introduction

1.1 Medicine Shortage

The European Medicines Agency and the Heads of Medicines Agency in 2019[1], defined medicine shortages as:

"A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level"

Medicine shortages are a global issue primarily affecting the patient, creating obstacles for health care professionals and competent authorities.[1]

The European Medicines Agency and the European Commission have been working together to prevent shortages and their impact. A task force on availability of authorized medicines was first introduced in 2016[2] and was piloted for three years as Single Point of Contact (SPOC) [3]network which meets on a monthly basis to discuss shortages reported by industry directly to the EMA, national medicine shortages experienced by member states and coordination of action to mitigate medicine shortages through early detection and notification.

[1] European Medicines Agency (EMA), Heads of Medicines Agencies (HMA). Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA) EMA/674304/2018. 2019 [cited on 2022 May 16] Available from URL : https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf

[2] HMA/EMA Task Force on availability of authorized medicines for human and veterinary use (TF AAM). 2016 [cited 2022 May 23] Available from URL: https://www.hma.eu/about-hma/working-groups/hma/ema-joint-task-force-on-availability-of-authorised-medicines-for-human-and-veterinary-use-tf-aam.html

[3] European Medicines agency. Availability of Medicines. [cited on 2022 May 25]. Available from URL: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines

1.2 Root Causes of Medicine Shortages

The pharmaceutical supply chain is complex and involves several stakeholders. Causes of shortages are multifactorial and range from delays or errors associated with placing orders, technical problems such as machine validation, natural disasters, quality related issues and manufacturing defects that would affect the safety and quality of the medicinal product. Unexpected demands due to the coronavirus outbreak recently caused shortages due to active ingredient export bans, medicinal product export bans, stockpiling due to the health crisis and logistical issues such as shipping. Shukar et al (2021) categorized medicine shortages into three main categories, supply issues, demand issues and regulatory issues based on previous studies conducted in the EU and United States (Malik et al., 2013; Hedman, 2016; Zu'bi and Abdallah, 2016; Schwartzberg et al., 2017; Walker et al., 2017; Jenzer et al., 2019). Lack of economic market attractiveness, diminishing demand for medicinal product, lower profitability, policy failures and market saturation are the key concepts behind shortages present in small countries like Malta.[4] Supply, demand and regulatory issues are discussed further in sections 1.2.1, 1.2.2 and 1.2.3.

1.2.1 Supply issues

Supply issues are multifactorial. Unavailability of raw materials, manufacturing problems, economic problems, quality problems in finished product, low market size and low-profit margins are just some examples of the supply issues (Dill and Ahn, 2014; Fox

[4] World Health Organization (WHO). Enhancing access to affordable medicine in small countries. 2017. [cited 2022 May 23]. Available from URL: https://www.euro.who.int/en/countries/malta/news/news/2017/07/enhancing-access-to-affordable-medicine-in-small-countries

and Tyler, 2017; Walker et al., 2017; Fox and McLaughlin, 2018; Phuong et al., 2019; Poulsen et al., 2021; Shukar et al, 2021).

During the Covid-19 pandemic, the most reported supply issue present in multiple countries was the shortage of raw active pharmaceutical products and excipients leading to manufacturing delays and subsequent medicine shortages.[5]

When a sole manufacturer or country is responsible for the manufacturing of a product, any manufacturing problem will lead to a supply issue. It is recommended that more than one source for active ingredients, excipients and finished medicinal products is present to mitigate medicine shortages and maintain market stability (Ventola, 2011 ; Coustasse et al, 2020 ; Shukar et al, 2021).

1.2.2 Demand Issues

During the Covid-19 pandemic, demand for drugs utilized in hospital stays such as anesthetics, immunosuppressants and analgesics increased substantially. Increased demand of these medicines could not be predicted or forecasted leading to significant medicine shortages.[6]

If medicines are procured through a tendering system, medicines are procured through one source, one supplier. If supplier cannot accommodate increase in demand the medicine will be in shortage. If one country has a sole supplier, MAHs and wholesalers who have not been awarded the tender will not have the product in stock leading to loss

[5] lnternational Pharmaceutical Federation (FIP). FIP addressing global medicine shortage. 2020 [Cited 2022 May 05]. Available from URL: https://www.fip.org/medicines-shortages

[6] European Patients Academy of Therapeutic Innovation. Medicine Shortages.[Internet]:2017 [Cited 2022 May 05]. Available from URL: https://www.maltahealthnetwork.org/wp-content/uploads/2017/07/Medicine- shortages-1.pdf

of market competition, availability of medicine and rise in prices (Dranitsaris et al, 2017; Shukar, 2021).

1.2.3 Regulatory Issues

European National competent authorities ensure that medicines placed on the market are of good quality, safety and efficacy. The Marketing Authorisation Holder (MAH) has the responsibility that any medicine placed on the market is in accordance with the terms of the authorisation.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) together with The Association of the European Self-Medication Industry (AESGP), The European Association of Euro-Pharmaceutical Companies (EAEPC), The European Industrial Pharmacists Group (EIPG), The European Healthcare Distribution Association (GIRP), Medicines for Europe and Vaccines Europe, released a position paper on medicine shortages, highlighting issues and possible solutions. Two main regulatory issues relating to medicine shortages were discussed; i) Time lag relating to time taken from start of registration application to end of process where authorization is issued and ii) national requirements, where certain member states require additional forms to be completed at a national level.[7]

1.3 Impact of Medicine shortages

Medicine shortages have not only a clinical impact but also an economic impact. Increased manpower is needed to investigate alternative agents, manage inventory and educate staff on proper use of alternative agents identified (Dill and Ahn, 2014; Fox,

[7] AESGP, EAEPC, EFPIA, GIRP, GPIE, Medicines of Europe, Vaccines Europe. Addressing the root causes of medicines shortages. Supply Chain Stakeholders' views on root causes and solutions. 2019 [cited May 16] Available from URL: https://www.efpia.eu/media/413378/addressing-the-root-causes-of-medicines-shortages-final-051219.pdf

2014, Phuong et al, 2019, Shukar et al, 2021). Impact of medicine shortages from a clinical and economic aspect is discussed in section 1.3.1 and 1.3.2. Impact of medicine shortages on healthcare professionals is discussed in section 1.3.3.

1.3.1 Clinical Impact of medicine shortages

The health and safety of the patient is always the priority in an effective health care system. Shortages of medicines lead to poorer treatment outcomes, delays in medical procedures, medication errors, alterations in treatment, prescription inaccuracies, prolonged hospital stay, adverse drug reactions and even in some instances patient death has been reported. (Becker et al, 2013; Mclaughlin et al, 2013; Dill and Ahn, 2014; Fox et al, 2014; Alsheikh et al, 2016; Mclaughlin et al, 2017; Rinaldi et al, 2017; Schwartzberg et al, 2017; Walker et al, 2017; Dave et al, 2018; Phuong et al, 2019, Shukar et al, 2021).

Use of less desirable and often more expensive alternative medicinal products impact the patient`s quality of life from a financial and health aspect (Musazzi et al, 2020).

Delayed or omitted medicine is the most reported medicine incident directly resulting from a medicine shortage (McLaughlin et al, 2013). Delayed or omission of medicine has been shown to increase risks of fatality or severe harm to the patient (Cousins et al, 2012).

1.3.2 Economic impact of medicine shortages

Medicine shortages result in more expensive alternatives therapies being suggested by healthcare professionals with the financial burden falling primarily on the patient. When

a medicine is in shortage the financial burden on the patient rises both due to the decreased availability of the product due to a high supply and demand, and due to the use of alternative more often expensive medicinal products. On the other hand hospitals and national health systems are impacted financially from the aspect of higher cost of medicinal product due to unavailability and manpower required to manage the shortage such as education sessions with regards to any changes in brand or strength of the alternative introduced due to medicine shortage and development of new policies to mitigate prospective medicine shortages (Fox and Tyler, 2013; Dill and Ahn, 2014; Fox et al, 2014; Mazer-Amirshahi et al, 2014; Costelloe et al, 2015; Hughes et al, 2015; Phuong et al, 2019; Atif et al., 2021; Shukar et al, 2021).

1.3.3 Impact of medicine shortages on patients and healthcare professionals

Hsia et al (2015) and Legido-Quigley et al (2019) evaluated patient perception on medicine shortages. Both authors reported that patients would like to be educated further on the impact of medicines shortage. Patients expressed feeling neglected by their primary healthcare provider and anxious when an alternative product was not established. Shortages give rise to patient frustration, unease with alternative therapy being suggested, dissatisfaction as well as psychological effects (Schwartzberg et al, 2017; Dave et al, 2018; Phuong et al, 2019; Shukar et al, 2021). Healthcare professionals have reported that medicine shortages increase workload in terms of seeking an alternative product to the medicine in shortage, loss of patient trust and strenuous patient-provider relationship (Hedman, 2016; Rinaldi et al, 2017; Walker et al, 2017; Phuong et al, 2019; Shukar et al, 2021).

1.4 Perception of patients and healthcare professionals on medicine shortages

The European Association of Hospital Pharmacists (EAHP) conducts a medicine shortage survey with hospital pharmacists every few years with several EU countries. In 2019 the medicine shortage survey by EAHP was extended to incorporate the perception of patients and healthcare professionals when experiencing medicine shortages during their care.[8] The perception of patient and of healthcare professionals in the EAHP study are summarized in sections 1.4.1 and 1.4.2.

1.4.1 Perception of Patients

In the EAHP[8] study, when facing medicine shortages in hospital the majority (55%) of the patients were not told the reason why medicine was in shortage. Healthcare providers offered three options when a medicine was in shortage: i) substitution of the medicine in shortage, ii) recommendation to miss a dose or iii) take a lower dose than the previously indicated dose. From the open comments present in the survey another option emerged where the patients stated they were advised to buy the medicine out of pocket from a pharmacy. When asked whether patients felt the shortage was tackled well, the majority of patients answered positively (71%) with 29% stating that they felt medicine shortage was not tackled to their satisfaction. The reasons given by patients for not being satisfied with options given where that i) they were abandoned ii) alternatives offered were not as effective iii) no alternative was located leading to a worsening in prognosis iv) exacerbation of condition and v) no information was given as to the reason why the medicine was in shortage. The work being carried out to ensure that shortage is mitigated in the future if any, was not communicated. The patients (N=68) believed that the shortage

[8] European Association of Hospital Pharmacists. (EAHP) 2019 EAHP Medicines Shortage Report. 2020 [cited 2022 May 16] available from URL: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf

did have an impact of their care at the hospital. Those patient who identified an impact stated that the medicine shortage caused, delays in care (N=30), treatment failure (N=18), increased hospital stay (N=18) and increased side effects from alternative medicine used (N=13).

1.4.2 Perception of Healthcare Professionals

Pharmacists, physicians, nurses and other healthcare professionals participated in the survey.[9] All the four groups of healthcare professionals stated that medicine shortages were a recurring problem in their hospitals. It was seen that the from previous survey conducted in 2017, the percentage of medicine shortages present grew by 5% (90% in 2017 and 95% in 2019). Reasons seen for shortage included shortage of active ingredient at a global scale, manufacturing problems, supply problems, pricing of a medicine, poor stock control and forecast of medicines, procurement procedures, stockpiling of medicines and increased demand for a specific product. When asked to how many times a medicine shortage was experienced due to sole supply from a single manufacture, hospital pharmacists and other healthcare professionals answered more than three times in one year.

1.5 Accessibility to medicines and medicines shortage

Accessibility to medicines and medicine shortages are connected. Medicine shortages impact the patient from a clinical, economical and humanistic aspect and creates a direct barrier to accessibility to medicines.[10]

[9] European Association of Hospital Pharmacists. (EAHP) 2019 EAHP Medicines Shortage Report. 2020 [cited 2022 May 16] available from URL: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf

[10] European Association of Hospital Pharmacists. EAHP Position Paper on Access to Medicines- Meeting the needs of patients! 2021 [cited 2022 May 16]. Available from URL: https://www.eahp.eu/sites/default/files/eahp_position_paper_on_access_to_medicines.pdf

1.5.1 Access to medicines

Saurman (2016) and Peters et al. (2018) state that

"Access enables a patient in need to receive the right care at the right time from the right provider and in the right place."

Accessibility to medicines can be further broken down into 6 aspects: acceptability, accessibility, adequacy, affordability, availability and awareness. Acceptability refers to patient satisfaction with the medicine and the healthcare provided rather than forced compliance. Accessibility refers to the medicine and service availability which also factors adequacy of supply. Adequacy of medicine and healthcare services refers to convenience for the patient and patient accepts the medicine as all patient centered aspects of the service and medicine are fulfilled. Affordability refers to the economic aspect of the medicine or healthcare service and availability refers to the adequate and acceptable provision of medicines and healthcare services (Muscat, 2020).

1.5.2 Barriers and enablers to medicine access

The European Association of Hospital Pharmacists (EAHP) published a position paper[11] in 2021 discussing barriers and enablers medicines access.

Enablers to medicines which are affordable, of good quality and are provided at the appropriate time include; i) Collaboration in between stakeholders involved with medicine shortages such as MAHs, government procurement, policy makers and the national competent authority, ii) Collaboration and best practice sharing of price reimbursement within different member states, iii) Increasing the use of preventive

[11] European Association of Hospital Pharmacists. EAHP Position Paper on Access to Medicines- Meeting the needs of patients! 2021 [cited 2022 May 16]. Available from URL: https://www.eahp.eu/sites/default/files/eahp_position_paper_on_access_to_medicines.pdf

measures such as adopting mitigation measures and improving early detection and notification of prospective shortages iii) Distribution of Health Technological Assessments (HTAs) which are reports detailing the therapeutic value of new innovative medicines, new diagnostic and treatment methods. The distribution of Health Technological assessments between member state have increase equity and even accessibility as they are used as a tool to share best practices thereby reducing duplicate research and supporting equal access to information.

Barriers to medicines which are affordable, of good quality and are provided at the appropriate time include; i) Unavailability of innovative medicines in different member states, leading to inequity between countries, ii) National pricing, reimbursement and tendering systems iii) Lack of purposeful procurement practices and iv) Medicine Shortages.

The paper[12] concluded that it is recommended that the expertise of hospital professionals in pharmaeconomics and biosimilars is utilized to introduce new innovative therapy thus enhancing access to medicines. EAHP also calls for prospective risk assessments investigating access and shortages related to lack of diversity in supply chain, adoption of medicine shortages mitigation measures as well as notification system to raise awareness on any impending medicine shortage to be tackled by the hospital in collaboration with stakeholders (Miljkovic et al, 2021).

[12] European Association of Hospital Pharmacists. EAHP Position Paper on Access to Medicines- Meeting the needs of patients! 2021 [cited 2022 May 16]. Available from URL: https://www.eahp.eu/sites/default/files/eahp_position_paper_on_access_to_medicines.pdf

1.5.3 Impact of medicine shortages on access to medicines

The impact of a medicine shortage on accessibility to medicines depends on four factors (Blankart and Felder, 2021). Incidence of shortage in question, duration of shortage, intensity of shortage and therapeutic and product areas affected.

In the study conducted by Blankart and Felder in 2021, a retrospective analysis of medicine shortages occurring in Switzerland was studied between 2015-2020. In 2019 alone, 238 events of medicine shortages were reported. The study also noted that during the peak of the Covid-19 pandemic demand for medicinal products was difficult to predict and spikes were witnessed. The incidence of a medicine shortage refers to the number of times a medicine was reported as in shortage or inaccessible to the patient. In this case over a period of 5 years 1336 market shortages were reported. The duration of a medicine shortage refers to the amount of days the product was absent from the market and inaccessible to the patient. Average duration of a shortage was 14 days. The intensity of the shortages refers to whether any other alternatives were also in shortage. The therapeutic and product area affected refers to whether a critical or essential drug is in shortage. One hundred and sixty-one essential medicines were reported in shortage although it is to be noted that Switzerland has a different essential medicine list than the World Health Organization (WHO).

1.6 Critical and essential medicines

Different members states and organizations refer to critical or essential drugs differently. The classification of a medicinal product or therapeutic group as critical can make a difference in how medicine shortages are tackled.

Anatomical Therapeutic Chemical (ATC)[13] groups can be used to follow medicine shortage criticality. Turbucz et al (2022) identified 4 ATC groups as critical medicine groups and studied medicine shortage notification, management and mitigation measures. The following four ATC groups were chosen and classified as critical if in shortage since all classes cause a significant impact on the patient in terms of delay in care, sub-optimal treatment and cancellation of care should they be in shortage; C: Cardiovascular, L: Antineoplastic and immunomodulating agents. J: Anti-infectives for systemic use, N: Nervous system agents.

Criticality of a product can be classified in a different manner according to the particular country or organisation making that classification.

1.6.1 Different country perspectives

Miljkovic et al (2020) analysed different countries risk assessments involving life-saving medications in shortage in different member states using drug classes. For France, Finland Bosnia and Herzegovina, Belgium, UK, Ireland and Austria, antibiotics as a therapeutic class was identified as critical and requires a prospective risk assessment should any medicine within the class be reported as in shortage. Austria, Greece and Romania and Montenegro identified Oncology medications as critical medicines. Austria, Belgium, Cyprus, France and Finland identified blood products and vaccines as critical medicines. Only Bosnia and Herzegovina and Finland identified Insulins as a critical medicine requiring prospective risk assessments. Oral anticoagulants and Diuretics were identified by Serbia to be a critical medicine. Nutritional liquids,

[13] World Health Organization Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD assignment.2022 [cited on 2022 May 16] Available from URL: https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/

adrenalin injections and antihypertensives were identified by Finland to be critical medicines. Israel recognizes that anesthetics are critical medicines that require a prospective risk assessment should any medicine within that class be reported in shortage.

1.6.2 World Health Organization- Essential Medicine List

The World Health Organization (WHO) defines essential medicines [14]as

"Medicines that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford. "

The essential medicines list is updated every two years with the intention to serve as a guide for countries, governments and competent authorities to always keep essential medicines stocks at hand. The list is issued as a guide as it does not consider the differences experienced on a national level in each individual country.

The latest version of the essential medicine list was published in 2021.[15] The list is divided in therapeutic classes summarized in Table 1.1 and contains all active ingredients the WHO deems as essential.

[14] World Health Organization (WHO). WHO Model Lists of Essential Medicines. [cited on 2022 May 15]. Available from URL: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

[15] World Health Organization (WHO). World Health Organization Model List of Essential Medicines. 22nd List (2021). 2021 [cited on 2022 May 16]. Available from URL: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

Table 1.1- WHO essential therapeutic classes list

Therapeutic Class	
Anesthetics	Medicines affecting the blood
Medicines for pain and palliative care	Diagnostic agents
Anti-allergic medication and medicines used in anaphylaxis	Antiseptics
Anticonvulsants and Antiepileptics	Diuretics
Immunomodulators and antineoplastics	Gastrointestinal medicines
Antiparkinsonism Medicines	Muscle Relaxants
Medicines for endocrine disorders	Ophthalmological preparations
Immunological	Medicines for reproductive and behavioral disorders
Vaccines	Medicines acting on the respiratory tract
Solutions correcting water, electrolyte and acid-base disturbances	Ear, nose and throat medicines
Vitamins and Minerals	Medicines for disease of joints
Dental preparations	Blood products

Table 1.1-Reproduced from: World Health Organization (WHO). World Health Organization Model List of Essential Medicines. 22nd List (2021). 2021 [cited on 2022 May 16]. Available from URL: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

1.6.3 European Medicines Agency definition of a Critical Medicine

The European Medicines Agency (EMA)[16] states that a definition of a critical product depends on two factors: Therapeutic use and Availability.

Therapeutic use makes reference to whether the product belongs to a class of drugs which are used in life-threatening situations where consequences to patient should medicine be unavailable would be high. Medicine can be used in both the acute setting or the long-term setting whereby chronic use of this medication has shown to increase prognosis and increase patient survival.

Availability refers to possible alternatives or substitutions for the medicine. Even though a medicine may be classified as critical due to its life-saving application, the availability of alternative medicines would render the product not critical.

Alternatives can be of different strength or formulation, alternative dosing schedules, availability of generics with the same active ingredient or therapeutic equivalent alternatives

1.7 Classification of a medicine shortage

Medicine shortages can be classified in a different manner according to the particular country or organisation making that classification. In a number of cases, classification of a medicine shortages depends on the impact of the shortage on patients and whether suitable alternatives are available. An example of a classification of a medicine

[16]European Medicines Agency (EMA) Criteria for classification of critical medicinal products for human and veterinary use. EMA/24304/2016. 2016 [cited on 2022 May 16] Available from URL:https://www.ema.europa.eu/en/documents/other/criteria-classification-critical-medicinal-products_en.pdf

shortage is one such classification based on that of EAHP[17] as summarised in Table 1.2. This classification categorises medicines shortages into four levels each level according to the impact to patient, from low to high. A description of each of these levels as given by the EAHP is also available in Table 1.2.

Table 1.2- European Association of Hospital Pharmacists' classification of medicine shortages

Level	Description
Level one (Low Impact)	Supply Problem with short duration where immediate available measures are sufficient and minimal additional management requirement
Level two (Medium Impact)	Supply Problem where alternatives in the same therapeutic class are available but require some management
Level three (High Impact)	Limited to no alternatives in same therapeutic class and require significant management. Medicines used in life-saving conditions or involving patient groups considered as vulnerable
Level four (Critical Impact)	No viable therapeutic alternatives, this triggers use of national resilience structures

Table 1.2- Reproduced from: European Association of Hospital Pharmacists. 2019 EAHP Medicines Shortage Report. 2020 [cited 2022 May 16] available from URL: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf

[17] European Association of Hospital Pharmacists. 2019 EAHP Medicines Shortage Report. 2020 [cited 2022 May 16] available from URL: https://www.eahp.eu/sites/default/files/eahp_2019_medicines_shortages_report.pdf

1.7.1 Different country perspectives

Turbucz et al (2021) studied the different classification of Critical shortages in Switzerland, Spain, Hungary, USA and Australia. Table 1.3 signifies the classification of a critical medicine shortage in different countries

Table 1.3- Classification of critical medicine shortages by different countries

Country	Classification of critical medicine shortage
Switzerland Spain Hungary	No alternatives present is automatically critical
USA	i) No alternatives present is automatically critical ii) Shortage risk index, ratio of unavailable to available alternatives. If ratio is higher than 5 it is a critical shortage
Australia	i) No alternatives present is automatically critical ii) Medicine in shortage has the potential impact to have a life-threatening impact on patient

Table 1.3 Reproduced from Turbucz B, Major M, Zelko R, Hanko B. Proposal for handling of medicine shortages based on a comparison of retrospective risk analysis. International Journal of Environment Research and Public Health. 2022; 19(7):1-15.

1.8 Medicine shortage mitigation strategies

Since risks incurred by the patient are high when facing medicine shortages, mitigation strategies to avoid medicine shortages should be in place to ensure a continuous supply and minimize the impact on the patient. [18] Responses and actions to mitigate and manage the medicine shortage is dependent on level of medicine shortage and impact on patient and healthcare system (Milijkovic et al, 2019) . Mitigation strategies can be categorized into enhancement of current operations, changes in government policies, management of current drug shortages and compulsory stockpiling present in sections 1.8.1 to 1.8.4.

1.8.1 Enhancement of current operations

One of the major problems associated with operations involving several stakeholders is lack of communication between said stakeholders. Increasing communication between stakeholders can mitigate medicine shortages (Fox et al, 2009) Communication can be between national competent authorities of EU member states, the national health system and competent authorities and MAHs with competent authorities. With a notification system in case of medicine shortage in place, a proactive and targeted approach can be taken to mitigate medicine shortages. Article 81 of the European Medicines Law Directive 2001/83/EC states that both Marketing Authorization Holders (MAHs) and distributors are responsible in ensuring continuous supply of medicines to meet patients' needs in each individual Member state.

Additionally, Article 23a and Article 27a of Directive 2001/81/EC states that if a product

[18] Scholz N. European Parliamentary Research Service. PE649.402. Addressing shortages of medicines. 2020 [cited on 2022 May 23]. Available from URL: https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649402/EPRS_BRI(2020)649402_EN.pdf

marketed supply is disrupted, the MAH will inform the competent authority of the member state which will be affected by the supply cessation. Ideally the notification should be made at least 2 months prior to planned market cessation or disruption or as soon as MAHs are aware of potential disruption. [19]

With this notification in place, the required information present such as medicine in shortage, reason for disruption and period of disruption is present to aid in the prioritization and mitigation of the medicine in shortage (Costelloe et al, 2015; Schwartzberg et al, 2017; Walker et al, 2017; Vogler and Fischer, 2020; Shukar et al, 2021)

1.8.2 Government policy

In order to mitigate medicine shortages, having good policies and programs in place can prevent or lessen impact of medicine shortages. Having a reserve stock in place or having a mandatory 6 months stock available can mitigate medicine shortages arising from manufacturing problems and supply disruption. During the Covid-19 pandemic, where threats to manufacturing were present for several medicines, further showed that these policies are required in each member state. The benefit of a good IT system would allow alerts should consumption increase and stocks available not suffice. Such alerts would allow the person responsible to take a proactive approach and prepare to find alternative routes and redistribute available stock (Shukar et al, 2021).

[19] European Medicines Agency (EMA), Heads of Medicines Agencies (HMA). Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA) EMA/674304/2018. 2019 [cited on 2022 May 16] Available from URL : https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf

1.8.3 Management of current medicine shortages

Redistribution of available stock, waste management, restrictions on current use stock and development of a medicine shortage unit are key concepts behind management of current shortages (Shukar et al, 2021).

Redistribution of available stock would involve prioritization of stock depending on severity of condition of patient and indication of the medicine. Waste management refers to the utilization of leftover drugs remaining after the dose has already been given to a patient. If small doses are administered and volume is left over, instead of throwing this away, it is kept for next patient or next appointment. A medicine shortage unit present in house at hospitals and institutions which would be responsible in identifying therapeutic equivalent medicines and focus on educating staff and clinicians with regards to waste management and prioritization of patients depending on risk is important to manage shortages, especially shortages related to critical medicines[20].

1.8.4 Compulsory Stockpiling

The Australian Government and the Australian Health Protection Principal Committee to guarantee access to essential medicines had created a National Medical stockpile[21] containing drugs, vaccines, antidotes and PPE to avoid critical shortages. The list is not

[20] European Healthcare Distribution Association, Medicine shortages in Europe and their impact on patients, a reflection paper. 2018 [cited 2022 Mar 24]. Available from URL: https://girp.eu/sites/default/files/documents/girp_medicine_shortages_reflection_paper.pdf

[21] Cook J. Therapeutic Goods (Medicines Watch List) Determination December 2018. 2018 [cited on 2022 May 16]. Available from URL : https://www.legislation.gov.au/Details/F2018L01679

available publicly. Switzerland [22] also follows a similar system where critical medicines are identified and are required to have three months stock at hand without the need to import medicines (Turbucz et al, 2022)

1.9 Risk tools to mitigate medicine shortage

A risk assessment exercise is necessary to analyze root causes of medicine shortages. Knowledge of causes behind medicine shortage would aid in forming risk mitigation measures (Acosta et al, 2019, Miljkovic et al, 2020). Risk mitigation measures vary from forming an essential medicine list unique to specific country needs, disclosure of supply disruptions as well as educating the public to avoid purchasing medicines facing shortages from online sources (Badreldin and Atallah, 2021)

Risk is the probability of an activity occurring that could cause an unwanted effect or harm (Calman and Royston, 1997; Muscat, 2020). In medicines shortages, risk relates to the occurrence of harm occurring to a patient should a medicine be in shortage (Poulsen et al., 2021). Risk may be quantified and applied prospectively and retrospectively to analyze the risks associated with a medicine shortage situation. This may be done through the utilization of the Risk Triangle. The Risk Triangle considers three aspects of risk, probability, severity or consequences and detectability of such a consequence occurring. Detectability can mitigate risks by reducing the occurrence of a consequence occurring (Attard Pizzuto, 2016; Muscat, 2020)

[22] SR 531.215.32. Verordnung Vom 12. August 2015 Über Die Meldestelle für Lebenswichtige Humanarzneimittel. 2013, [cited on 2022 May 16]. Available from URL https://www.fedlex.admin.ch/eli/cc/2015/544/de

1.9.1 Risk assessments

Failure Mode and Effects Analysis (FMEA) is a commonly used tool that identifies all possible failures and prioritizes failures according to the severity of consequences arising from the failure. This proactive tool is essential for calculating potential impacts on patients arising from medicine shortages (Williamson et al 2009, Macdonald E 2011, Anjalee et al 2020) as well as medicine safety in hospitals by identifying risks in processes. FMEA is utilized to measure the probability of a shortage occurring, and should it occur, the severity of consequences to get a risk score by which prioritization can take place to benefit the patient.

A study in Denmark (Poulsen et al, 2021) created a 4x4 risk matrix. Classification of the severity relating to medicine shortages and the probability was done through a survey to the national, regional and local level stakeholders in Denmark. Information was then compiled into a risk matrix, table 1.4 shows the classification reached by the focus group.

Table 1.4- Classification of categories of risk to patient

Classification	Consequence to Patient
Minor	No or minimal patient consequence
Moderate	Simple treatment or increased hospitalization stay by 1 day
Major	○ Permanent lessening of bodily functioning ○ Significant increased treatment in one patient ○ Increased length of stay for a minimum of 3 patients
Catastrophic	○ Death ○ Major permanent loss of bodily functioning/disability for one patient

Table 1.4 Reproduced from:Poulsen J.H, Clemmensen M, Norgaard L, Dieckmann. Prospective risk assessments of patient safety events related to drug shortages in hospitals: Three actor-level perspectives. Exploratory Research in Clinical and Social Pharmacy. 2021; 3

Probability was classified as remote (every second year), uncommon (yearly), occasional (every third month) and frequent (every month)

The study highlighted the shortcomings of a failure mode and effects analysis, and that context must be applied before taking a decision solely based on the results obtained from the risk matrix tool. Use of a decision tree based on the findings of the risk matrix to triage medicine shortages and determine criticality of medicine shortage is essential to provide context to the situation. Risk matrices do not provide a complete solution but may be used as an initial state in a decision-making tree.

1.10 Medicines shortage scenario in other countries

Medicine shortages have been increasing in USA (Ventola L, 2011) and France (Traore et al., 2021) prior to Brexit and the Covid-19 pandemic.

In a 6-year retrospective study held in France, 2019 reported the most shortages from the previous 5 years with 305 reported shortages. The most frequent ATC classes in shortage were N (nervous system class), J class (anti-infectives for systemic use), C class (cardiovascular medicines) and the L class (antineoplastic and immunomodulating agents).

Similarly in the USA, FDA reported in 2011 that oncology medications, injectable drugs and generic drugs were the most reported in shortage in 2011 (Ventola L, 2011). In order to mitigate these shortages, importation of foreign products was allowed by the FDA[23]. In 2010 the FDA was able to mitigate shortages by early detection and initiating discussion with pharmaceutical manufacturers.

1.11 The local medicine shortage scenario

Malta has relied heavily on the United Kingdom to obtain medicines as the packaging of the medicine manufactured in the United Kingdom would already be in the English language and would not require translation. One hundred and forty-three parallel import licenses and one thousand two hundred and ninety Article 126a authorisations were issued for products being sourced from the United Kingdom.[24] In 2020, the United Kingdom left the European Union with the consequence that medicines can no longer be imported and distributed in the European member states. During the Covid-19 pandemic, increase in demand of critical medicines was seen

[23] Stein R. Shor tages of key dr ugs endanger patients. The Washington Post. 2011 [cited on 2022 May 16}. Available at URL www.washingtonpost.com/na- tional/shor tages-of-key-dr ugs-endanger-patients/2011/04/26/ AF1aJJVF_story.html?hpid=z5.

[24] Farrugia C. Malta: preparations for the impact of Brexit on the pharmaceutical supply chain in Malta- The perfect storm. PharmaWorld. 2018 [cited on 2022 May 16] Available from URL: https://www.pharmaworldmagazine.com/preparations-for-impact-of-brexit-pharmaceutical-supply-chain-malta/

globally including in Malta. Malta has had to rely on Article 20 exemption in order to mitigate medicine shortages that would have a significant impact, clinically and financially on the patient.

Article 20 is an emergency exemption in accordance with the Medicines Act Chapter 458 of the Laws of Malta, which is granted by the Licensing Authority, under guidance from the Malta Medicines Authority for a medicinal product not currently holding a marketing authorization under strict exceptional cases. The exemption is subject to pre-determined conditions and requires Medicines Authority to review each Article 20 exemption[25]application on a case-by-case basis.

[25] Article 20 of Chapter 458 of the Laws of Malta (Medicines Act) [Cited 2022 May 4] Available from URL: https://legislation.mt/eli/cap/458/eng/pdf

1.12 Rationale for the research

Medicine shortages impact the patients, healthcare professionals and national health systems. The consequences experienced by patients when a medicine is in shortage are significant and a proactive approach is required to mitigate such shortages. Studying the perception of healthcare professionals and patients when experiencing medicine shortages at the community setting will aid in policy and decision making. Malta has had to rely on Article 20 exemption to maintain medicines stock position and avoid out of stock of critical medicines. Evaluating the rationale and generating trends observed from Article 20 exemptions granted will determine medicines most likely to be in shortage prospectively whereby mitigation of such shortages can be carried out nationally. Not granting an Article 20 exemption might have significant consequences on the patient. Developing criteria to measure risk of not granting an Article 20 exemption is a crucial first step in the decision on whether an Article 20 exemption should be granted for a justified public health reason for the sole humanitarian reason not to leave patients without medicine.

1.13 Aims and Objectives

The aims and objectives of this study are to (i) study the perception of healthcare professionals and patients when facing medicine shortages in the community setting (ii) evaluate the rationale of exemption from registration due to a justified public health need in accordance with Article 20 of the Medicines Act Chapter 458 of the Laws of Malta (iii) develop criteria to classify and measure risk associated with evaluating an application for an Article 20 exemption to enhance accessibility to medicines.

Chapter Two

Methodology

2.1 Research Overview

The study methodology was divided into three different studies in order to reach the aims and objectives of the study: 1) To investigate the perception of family doctors, pharmacists and patients when facing medicine shortages in the community pharmacy setting, three questionnaires were developed, 2) To evaluate the rationale of granting an Article 20 exemption in accordance with the Medicines Act Chapter 458 of the laws of Malta, retrospective analysis on Article 20 exemption applications was carried out and 3) To develop criteria to classify and measure risk with evaluating an application for an Article 20 exemption to enhance accessibility to medicines, focus group was assembled and categorization and criteria was discussed.

2.2 Research Setting

The research was conducted at the Medicines Intelligence and Access Unit (MIAU) within the Malta Medicines Authority. The MIAU maintains a patient center approach and facilitates access to medicines through the proactive compilation of drug intelligence and dialogue with several stakeholders.[26]

2.3 Research Design- Study 1

To study the perception of pharmacists, family doctors and patients when facing medicine shortages, the methodology summarised in Figure 2.1 was followed

[26] Malta Medicines Authority. 2021 [cited on 2022 May 24] Available from URL: https://medicinesauthority.gov.mt/directoratesunits?l=1

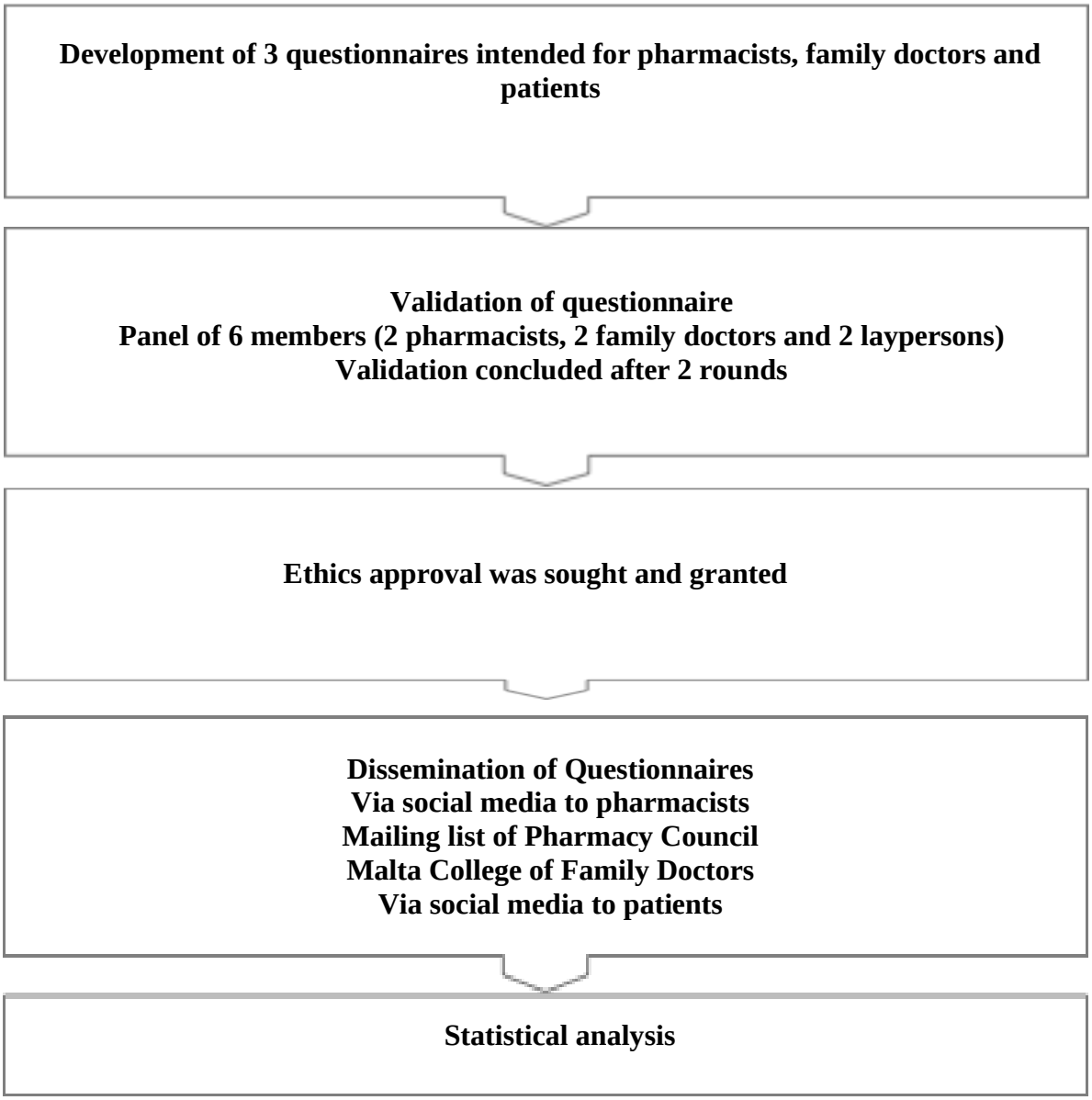

Figure 2.1- Study 1 methodology overview

2.3.1 Development of questionnaires

To study the experience of family doctors, pharmacists and patients with medicine shortages from a community pharmacy, questionnaires were developed. The questionnaire intended for family doctors (appendix 5) contained physician background and experience with medicine shortages in the community pharmacy setting. The pharmacist questionnaire (appendix 6) was split into three sections. pharmacists background, experience with shortages in the community pharmacy setting

and experience with medicine shortages from the Pharmacy Of Your Choice (POYC) scheme.[27] The patient questionnaire (appendix 7) was split into three sections: patient demographics, experience with shortages in the community pharmacy setting and experience with medicine shortages from the Pharmacy Of Your Choice (POYC) scheme. The patient questionnaire, developed in English, was translated to Maltese and back translated to English language to ensure language correctness. Online versions for each questionnaire were created using Google Forms.

2.3.2 Validation of questionnaires

In order to validate the questionnaires, a validation tool was created where panelists could indicate on a Likert scale the readability and clarity of the questions chosen and whether any questions were missing from the questionnaire. A panel of 6 members consisted of 2 pharmacists, 2 family doctors practicing within a community pharmacy and 2 laymen were recruited by convenience sampling to validate the developed questionnaires. The questionnaire for patients was revised once when a member of the validation panel pointed out that substitution of a scientific term would make the questionnaire easier to understand for the patient.

2.3.3 Ethics approval

To apply for ethics approval a patient consent form was developed in both the English and Maltese language. A patient information leaflet was developed in both the English and Maltese language. A managing pharmacists form was developed to be signed by the managing pharmacists that allowed the physical dissemination of the questionnaires. A covering letter was developed for family doctors to give background research on the study being conducted.

[27] Pharmacy Of Your Choice Scheme [cited on 2022 May 24]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/Poyc-scheme.aspx

An approval from the Faculty of the Medicine and Surgery Research Ethics Committee was obtained (appendix 1), the questionnaire was disseminated to pharmacists, patients and family doctors both through the online platform- Google Forms and through physical dissemination through convenience sampling. The questionnaires were disseminated between 20th March and 20th May (2 months). The questionnaire for pharmacists was disseminated: 1) online via the social media group 'Maltese pharmacists and pharmacy students' (n=508) 2) through the mailing list of the Pharmacy council whish was sent out to every registered pharmacist in Malta. The questionnaire for family doctors was disseminated through the mailing list of the Malta College of Family Doctors (n=300). The patient questionnaire was disseminated 1) online via social media group 'The Salott' (n=62,000) 2) through the physical dissemination from one community pharmacy situated in Hamrun Malta.

2.4 Research Design- Study 2

To evaluate the rational of the granting of an Article 20 exemption, the method followed consisted of:

1) Training with regards to the legal background of Article 20 exemption and current process of tackling Article 20 exemption applications
2) Retrospective data gathering of previous applications received which were either approved or rejected
3) Development of a database
4) Generation of trends seen in Article 20 exemption approvals granted between October 2020 and March 2022 (18 months).

2.4.1 Article 20 exemption training

Training was carried out during the month of August 2021 by the Head of the Medicines Intelligence and Access Unit (MIAU) within the Malta Medicines Authority (MMA). The training sessions were divided into 3 hour-long sessions and consisted of the 1) legal basis of the Article 20 exemption 2) Explanation of documents and evidence required to be collected in order for the exemption application to be processed 3) Processing of an application from start to finish including a positive recommendation to the Licensing Authority to grant an Article 20 exemption for a medicine.

2.4.2 Retrospective data gathering

Article 20 exemption application are received through email communication with the Medicines Authority. Data was gathered for applications received between October 2022 and March 2022 and categorized as accepted or rejected.

2.4.3 Data extraction and generation of trends

An Article 20 exemption database was developed to standardize data gathering and extraction using Microsoft Excel®. The database created contains 44 sections including reason for requesting a permit, source country, considerations, conditions of exemption, status of application, ATC Code and Therapeutic class. A quantitative approach was adopted to generate trends seen in Article 20 exemption applications approved between October 2020 to March 2022 using Microsoft Excel®.

2.5 Research Design- Study 3

To develop criteria to classify risks associated with not granting Article 20 exemption a focus group discussion was held to acquire knowledge and expertise of patient impact should an Article 20 exemption not be granted.

2.5.1 Focus Group set-up

The focus group was used to classify and categorise risk severity and risk probability relating to patient impact should an Article 20 exemption not be granted. The expert panel consisted of 1 clinical practitioner and 9 pharmacists, 4 of which were Article 20 exemption application reviewers. The aim of the focus group was to classify and categorize risk severity and risk probability to the patient by use of a risk matrix, should an Article 20 exemption not be granted.

An email communication was sent to gathered interest in virtual focus group participation and to confirm their attendance should they wish to participate in the focus group to discuss the risks and patient impact should an Article 20 exemption not be granted.

An extensive literature review was carried out to compare previous risk assessments. The World Health Organization guidelines on quality risk management[28] was consulted to be included as part of the background and introduction to the Focus Group. The Risk based approach for prevention and management of drug shortages by the parenteral drug association was consulted to study the different levels of impact and severity medicine shortages have on patients.[29]

[28] World Health Organization. WHO guidelines for quality risk management. 2013. [cited on 2022 May 25]. Available from URL: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf

[29] Ramnarine E, Jornitz M, Long M, O'Donnell K, Ronninger S, Smalley C et al. Technical Report no 68. Risk-based approach for prevention and management of Drug shortages. 2014.[cited on 2022 May 25]. Available from URL: https://store.pda.org/TableOfContents/TR68_TOC.pdf

The focus group was led by the researcher who prompted a discussion. The focus group consisted of:

1. Introduction

   The expert panel were introduced and the researcher presented a brief 5 minute presentation (appendix 13) and went over the background of medicine shortages, impact of shortages to patient, risk-based analysis and the aim of the focus group explained that the aim of the focus group discussion to define classification of risk probability and severity related to the not granting an Article 20 exemption

2. Discussion

   The researcher focused on obtaining expertise from the focus group panel with regards to risks associated with the not granting of an Article 20 exemption and the risks included with granting an Article 20 exemption. In step 2 it was discussed that a retrospective analysis is carried on previously approved Article 20 exemptions to further clarify the classifications.

3. Closure

   The researcher provided a summary of the main outcomes of the discussion.

For focus group discussion round 2, a retrospective analysis was carried out to pilot the classification of risk severity by analysis from previously approved Article 20 exemptions at the MIAU between October 2020 to March 2022.

1. Introduction

   The researcher presented a short presentation (Appendix 14) and applied real case scenarios of medicines which fit the criteria and classification previously discussed. The criteria and classification of risk probability and risk severity were accepted by the panel.

2. Discussion

The researcher promoted a discussion with regards to the risk critical numbers to better accurately risk critical ranges derived from the risk matrix to categorize risk as high, medium and low risk

3. Closure

The researcher provided a summary of the main outcomes of the discussion and completed risk tool which was validated through the focus group discussion.

Chapter Three

Results

3.1 Study 1 results

To study the perception of family doctors, pharmacists and patients when facing medicine shortages in the community, three questionnaires were developed. The family doctor questionnaire (Appendix) contained 12 questions, 9 closed ended questions and 3 open ended questions which were divided into 2 sections: physician background and experience with shortages from community pharmacy. Questionnaire was available in English language only. The pharmacist questionnaire (Appendix) contained 17 questions, 13 close ended questions and 4 open ended questions divided into 3 sections: pharmacists background, experience with shortages from community pharmacy, experience with shortages from medicines obtained through the POYC scheme. Questionnaire was available in English language only. The patient questionnaire (Appendix) contained 19 questions, 15 close ended questions and 4 open ended questions divided into three sections: patient background, experience with shortages from community pharmacy, experience with shortages from medicines obtained through the POYC scheme. Questionnaire was available in both the Maltese and English language.

3.1.1 Results from family doctor questionnaire

Twenty family doctors answered the questionnaire. From the 20 family doctors who answered the questionnaire, 6 were between the ages of 18-30 years, 1 was between the ages of 31-40 years, 5 were between the ages of 41-50 years, 4 were between the ages of 51-60 years and 4 were more than 60+ years. From the 20 family doctors who answered the questionnaire, 13 were female and 7 were male. When asked about years of experience in community, 2 doctors answered less than 2 years, 4 doctors answered more than 2 years but less or equal to 5 years, 4 doctors answered more than 5 years but less or equal to 10 years and 10 doctors answered more than 10 years of experience working in the community. For the question relating to locality of practice, the responses were converted from individual hometowns to the National Statistics Office Malta

(NSO) districts. categories [30]. Nine doctors practiced in the Northern Harbour districts, 6 doctors practiced in the Northern districts and 5 doctors practiced in the South Harbour districts.

When asked whether family doctors experienced medicine shortages in the community not related to POYC 90% of the respondents answered in the positive with only 10% answering in the negative. Figure 3.1 exhibits the ratio of positive to negative responses.

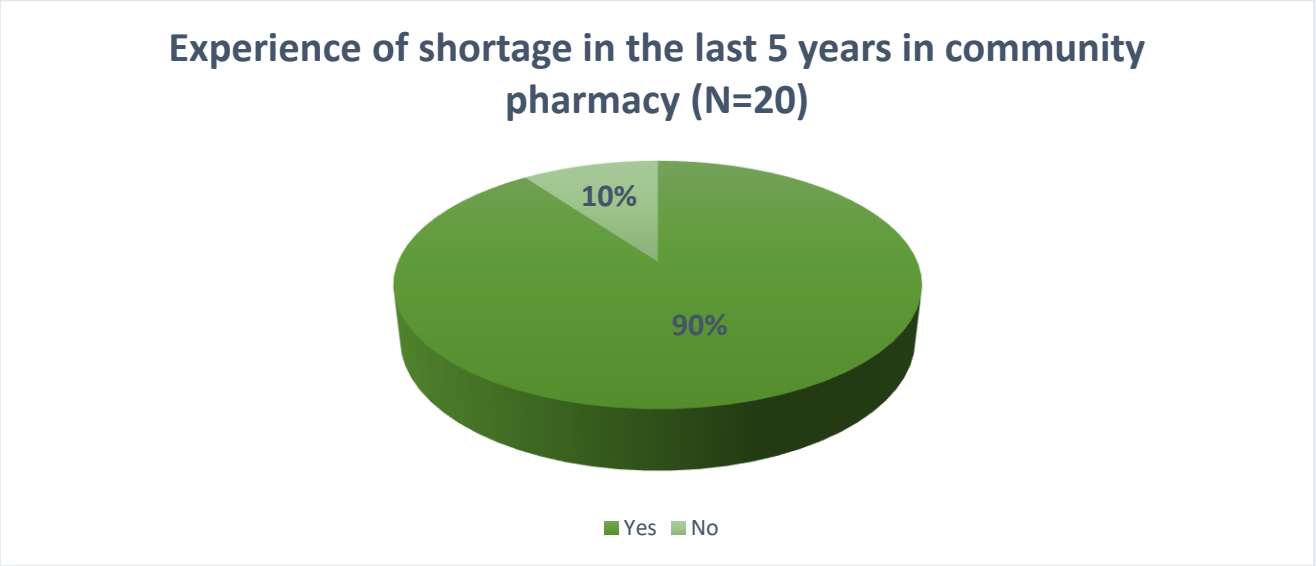

Figure 3.1 Experience with medicine shortage from a community pharmacy

When asked how the family doctors were made aware of the shortages through a multiple-choice question, 3 doctors answered from agent/wholesaler, 3 doctors were made aware from pharmacists, 5 doctors were made aware of medicine shortage from patient, 5 doctors answered from medical representatives and 2 doctors answered from news articles. When asked about the most frequent therapeutic class of medicines was in shortage through a multiple-choice question where the respondents could tick more than one answer, 9 doctors answered hormonal preparations and respiratory system respectively, 7 doctors answered vaccines and dermatologicals respectively and 4 doctors answered gastro-intestinal medications and genito-

[30] National Statistics Office (NSO). Regional Statistics Malta. 2019 Edition. [cited 2022 May 23]. Available from URL: https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/02_Regional_Statistics_(Gozo_Office)/Regional%20Statistics%20MALTA%202019%20Edition.pdf

urinary system medications respectively. A summary of most frequent medicines in shortage experienced by family doctors is found in the Figure 3.2:

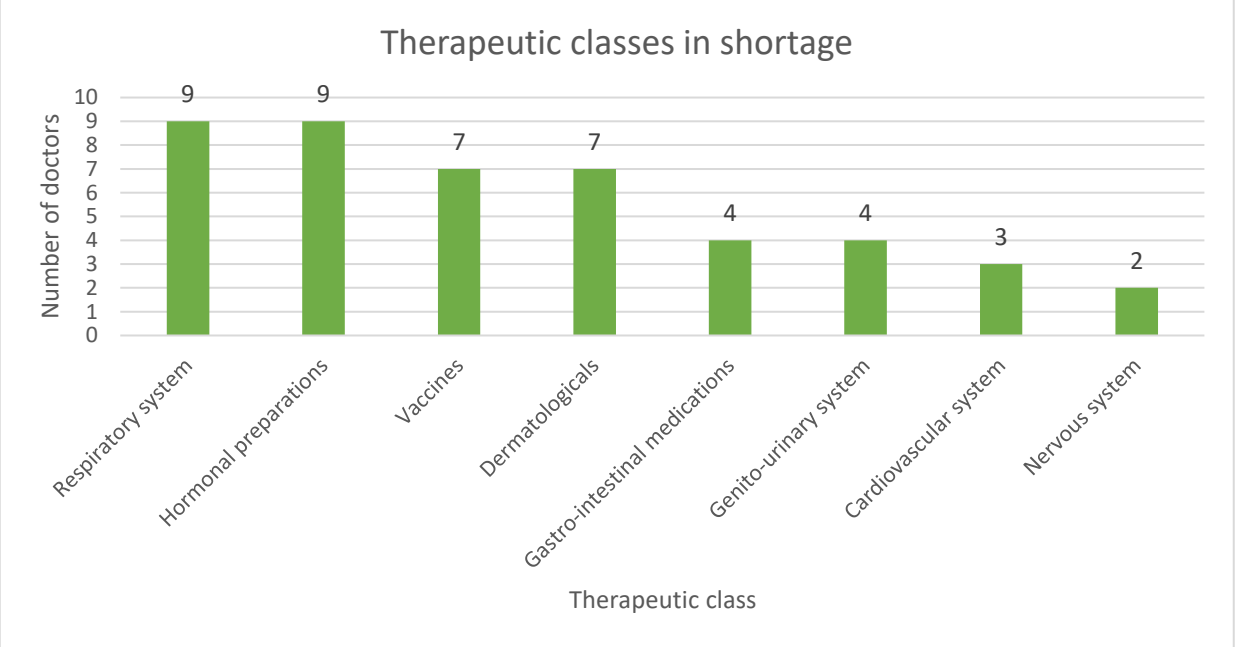

Figure 3.2-Most therapeutic classes experienced to be in shortage

When asked which solution was offered to the patient in case of medicine shortage through a multiple-choice question where respondents could tick more than one answer, 14 doctors stated offered substitution of medicine with an alternative, 15 doctors referred patient to another pharmacy, 1 answered provision of a lower dose. It was noted that no doctor answered that patient was advised that missing or skipping a dose is necessary as a solution in case of medicine shortage. Most doctors (n=19) answered in the positive when asked whether there was any collaboration with the pharmacist when medicine required for patient treatment was in shortage, with only one doctor answering in the negative. When asked about impact on patient when medicine was in shortage through use of a multiple-choice questionnaire where respondents could tick more than one answer, 12 reported sub-optimal treatment, 11 reported increase in expense to patient and caused distress and inconvenience, 9 reported cancellation of care, 8 reported delays in care, 6 reported medication error and 5 reported greater toxicity to patient. Figure 3.3 shows a summary of impact of medicine shortages on patient care identified through the research.

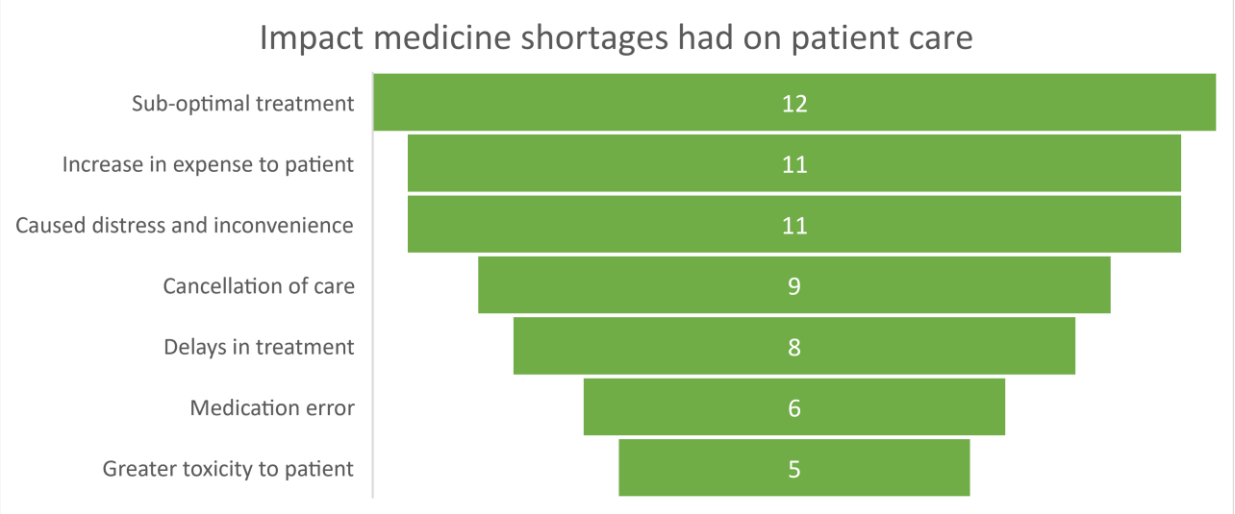

Figure 3.3- Impact medicine shortages had on patient care

When the family doctors were asked to list medicines which they experienced to be in shortage in the last 5 years in their community practice the following medications in table X below were mentioned.

Table 3.1- Medicines reported to be in shortage by family doctors

Medicines reported to be in shortage		
Solupred®	Renil®	Zoely®
Foradil®	Visanne®	Verkazia®
Flixotide®	Ditropan®	Cosopt®
Rectodelt®	Panadol Actifast®	Nurofen®
Actifed Cough Linctus®	Airbufo®	Engerix®
Rhinathiol Cough Linctus®	Ketrel®	Gavsicon Syrup® and Tablets®

3.1.2 Results from patient questionnaire

The questionnaire intended for patients was available in both English and Maltese language. From the 200 responses received, 166 responses were in the English language and 34 responses were in Maltese. For ease of reference the descriptive statistics will be presented as one figure. From the 200 patients who answered the questionnaire, 55 were between the ages of 18-30 years, 52 was between the ages of 31-40 years, 41 were between the ages of 41-50 years, 33 were between the ages of 51-60 years and 19 were more than 60+ years.

From the 200 patients who answered the questionnaire, 170 were female and 30 were male. When asked about highest level of education achieved, 4 patients answered less than primary level, 24 patients answered secondary level, 83 patients answered tertiary level and 89 patients answered post-graduate level. For the question relating to locality of residents, the responses were converted from individual hometowns to the National Statistics Office Malta (NSO) regional categories.[31] Ten patients were from the Gozo and Comino District, 53 patients were from the Northern district, 57 patients resided in the Northern Harbour district, 33 patients resided in the Southeastern district, 27 patients resided in the South Harbour region and 20 patients resided in the Western district.

When asked whether patients experienced medicine shortages in the community not related to POYC 116 of the respondents answered in the positive with 84 patients answering in the negative. Figure 3.4 exhibits the ratio of positive to negative responses.

[31] National Statistics Office (NSO). Regional Statistics Malta. 2019 Edition. [cited 2022 May 23]. Available from URL https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/02_Regional_Statistics_(Gozo_Office)/Regional%20Statistics%20MALTA%202019%20Edition.pdf:

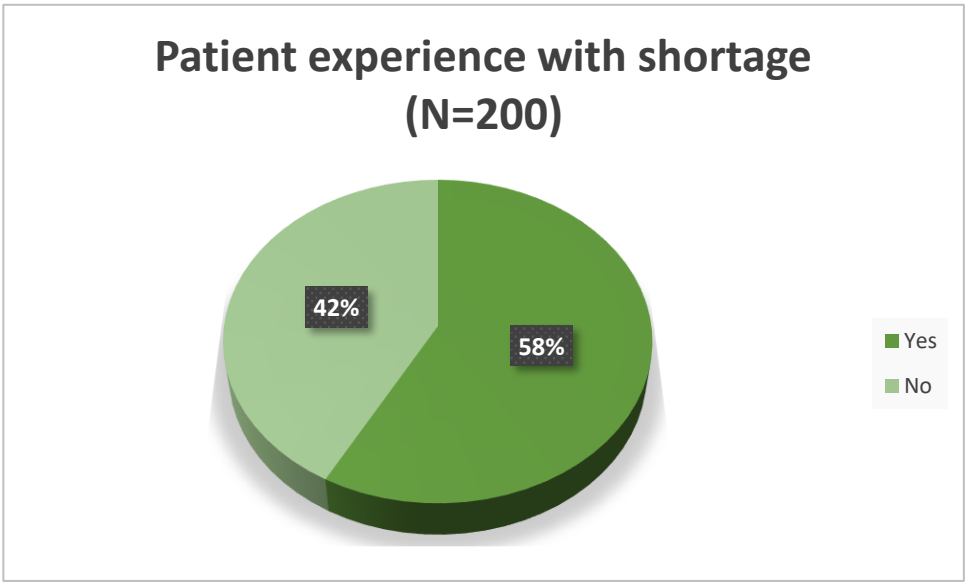

Figure 3.4- Experience with medicine shortage from a community pharmacy

When the patients were asked with regards to solution offered by pharmacist 92 patients answered substitution of the medicine, 36 patients were referred to doctor or prescriber, 19 were referred to another pharmacy and 1 patient was advised that skipping or missing a dose was necessary. Seventy-two patients answered in the negative when asked whether medicine was solved to their satisfaction and 48 patients answered in the positive. The patients who answered in the negative were then asked reasons why medicine was not solved to their satisfaction through a multiple-choice question where respondents could tick more than one option. Forty-nine patients stated that alternative medicine suggested was not as effective as the medicine in shortage, 29 patients answered that no alternative for medicine in shortage was available, 16 patients stated that medicine suggested as alternative caused unwanted side effects and 10 patients stated that medicine suggested as alternative was higher in price. Figure 3.5 shows a summary of the reasons why medicine shortage was not solved to the patient's satisfaction.

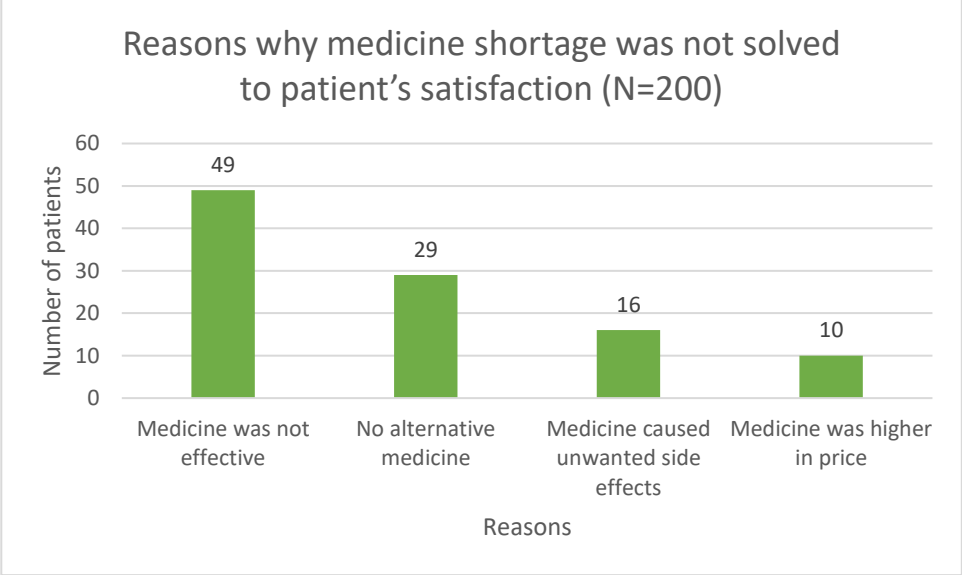

Figure 3.5- Reasons why medicine shortage was not solved to patient's satisfaction

In case of medicine in shortage, patients were asked what the difference in price between medicine in shortage and alternative. Sixteen patients stated that difference in price was of 1 Euro, 73 patients stated that difference in price was between 1 Euro and 5 Euro, 8 patients stated that difference in price was more than 5 Euro and 5 patients stated that difference in price was more than 10 Euro. Figure 3.6 summarises the difference in price between medicine in shortage and alternative being recommended.

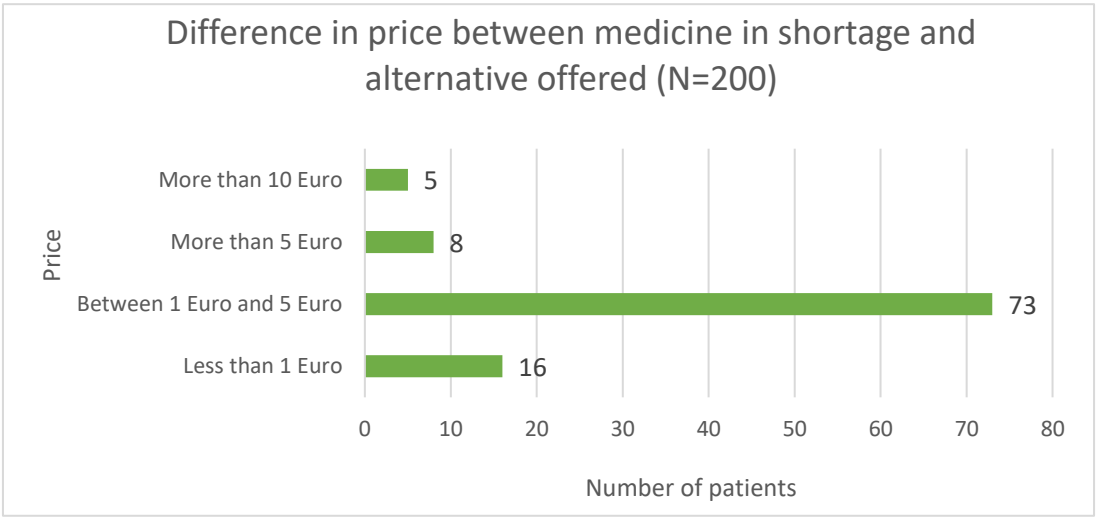

Figure 3.6-Difference in price between medicine in shortage and alternative offered

When patients were asked for how long they had to buy the medicine in shortage 49 patients stated between 1 to 3 months, 18 patients stated more than 3 months, 4 patients stated more than 5 months and 26 patients stated they had to buy the alternative medicine for more than one year.

When the patients were asked to list medicines which they experienced to be in shortage in the last 5 years from their community pharmacy, unrelated to medicines obtained through the POYC scheme, the following medications in table 3.2 were mentioned.

Table 3.2- Medicines reported in shortage by patients from community pharmacy

Medicines reported to be in shortage				
Solupred®	Osteogel®	Dentinox®	Telfast®	Zoely®
Foradil®	Visanne®	Neoclarityn®	Motilium®	Uniflu®
Qlaira®	Yaz®	Nurofen Plus®	Calpol®	Moment®
Rectodelt®	Panadol Actifast®	Feminax®	Fybogel®	Solpadeine Migraine®
Actifed Cough Linctus®	Glucophage®	Bonjela®	Zomig®	Solpadeine Soluble®
Rhinathiol Cough Linctus®	Lemsip®	Clarinase®	Canesten Oasis®	Gavsicon Tablets®
Zantac®	Cosopt®	Day Nurse® syrups	Fosteo®	Night Nurse® syrup
Gavsicon Syrup®	Nurofen®	Sunya®	Coltramyl®	Medofed® compound

When patients were asked whether they have experienced medicine shortages from the national health system Pharmacy of Your Choice scheme (POYC), 30 patients answered in the positive and 170 patients answered in the negative. Solution offered by pharmacist in case of shortage

included substitution of the medicine for 19 patients, advised that missing or skipping a dose is necessary for 2 patients, referred to doctor for 11 patients and 22 patients purchased the medicine from the pharmacy when it was out of stock from the POYC scheme. When asked whether medicine shortage was solved to their satisfaction, 26 patients stated it was not solved to their satisfaction and 4 patients stated it was solved to their satisfaction. The patients which stated that medicine shortage was not solved to their satisfaction where asked reasons why medicine shortage was not solved to their satisfaction through use of a multiple-choice question were more than one reason can be ticked. Medicine suggested as substitute was higher in price was the most reported reason with 15 patients, alternative medicine was not as effective as medicine in shortage was the second most common reason with 9 patients followed by no alternative was available for 7 patients and medicine suggested as substitute caused unwanted effect with 6 patients. Figure 3.7 shows a summary of the most reported reasons medicine shortage through the POYC was not solved to their satisfaction.

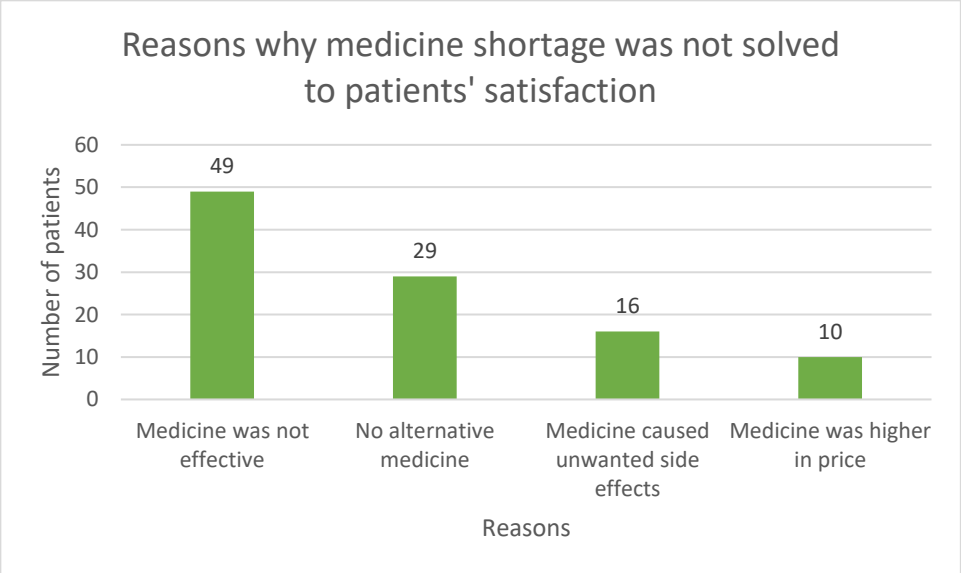

Figure 3.8- Reasons why medicine shortage was not solved to patients' satisfaction

When asked about the difference in price between medicine in shortage and alternative medicine suggested, 10 patients stated between 1 Euro and 5 Euro, 10 patients stated more than 5 Euro and 10 patients stated more than 10 Euro. From the 30 patients which experienced shortage through the POYC scheme, 17 had to buy the alternative medication between 1 to 3 months, 3 patients for more than 3 months, 4 patients for more than 5 months and 6 patients for more than one year.

When the patients were asked to list medicines which they experienced to be in shortage in the through the POYC scheme, the following medications in table 3.3 below were mentioned.

Table 3.3- Medicines reported by patients were in shortage from the POYC scheme

Medicines reported in shortage		
Mesalazine 400mg tablets	Simvastatin 20mg tablets	Lactulose syrup
Metformin 500mg tablets	Bumetanide 1mg tablets	Betamethasone ointment
Clobetasol scalp application	Beclomethasone inhaler	Paroxetine 20mg tablets

3.1.3 Results from pharmacists questionnaire

Fifty community pharmacists answered the questionnaire. From the 50 pharmacists who answered the questionnaire, 20 were between the ages of 18-30 years, 10 was between the ages of 31-40 years, 10 were between the ages of 41-50 years, 5 were between the ages of 51-60 years and 5 were more than 60+ years.

From the 50 community pharmacists who answered the questionnaire, 30 were female and 20 were male. When asked about years of experience in community, 5 pharmacists answered less than 2 years, 10 pharmacists answered more than 2 years but less or equal to 5 years, 15 pharmacists answered more than 5 years but less or equal to 10 years and 20 pharmacists answered more than 10 years of experience working in the community. For the question relating to locality of practice, the responses were converted from individual towns to the National Statistics Office Malta (NSO) districts.[32] Ten pharmacists practiced in the Northern Harbour districts, 30 pharmacists practiced in the Northern districts, 5 pharmacists practiced in the South Harbour districts and 5 pharmacists practiced in the Western district.

When asked whether community pharmacists experienced medicine shortages in the community not related to POYC all the respondents answered in the positive (n=50). When asked how the community pharmacists were made aware of the shortages through a multiple-choice question, 34 pharmacists answered from agent/wholesaler, 5 pharmacists were made aware of medicine shortage from patient, 4 pharmacists answered from medical representatives, 4 pharmacists answered from news articles, 1 pharmacist answered from family doctor, 1 pharmacist answered from managing pharmacists and one pharmacist answered from collogues at work. When asked about the most frequent therapeutic class of medicines was in shortage through a multiple-choice question where the respondents could tick more than one answer, 12 pharmacists answered medicines used for respiratory system, 11 pharmacists stated vaccines, 9 pharmacists stated medicines used for the gastro-intestinal system and the hormonal system respectively, 7 pharmacists stated medicines used in cardiovascular system were noted to be in shortage and 4 pharmacists stated that medicines used for nervous system, anti-infective medicines, muscoskeletal medicines, dermatological preparations, cough and cold preparation and eye

[32] National Statistics Office (NSO). Regional Statistics Malta. 2019 Edition. [cited 2022 May 23]. Available from URL: https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/02_Regional_Statistics_(Gozo_Office)/Regional%20Statistics%20MALTA%202019%20Edition.pdf

preparation were in shortage respectively. A summary of most frequent therapeutic classes in shortage experienced by pharmacists is found in the Figure 3.8:

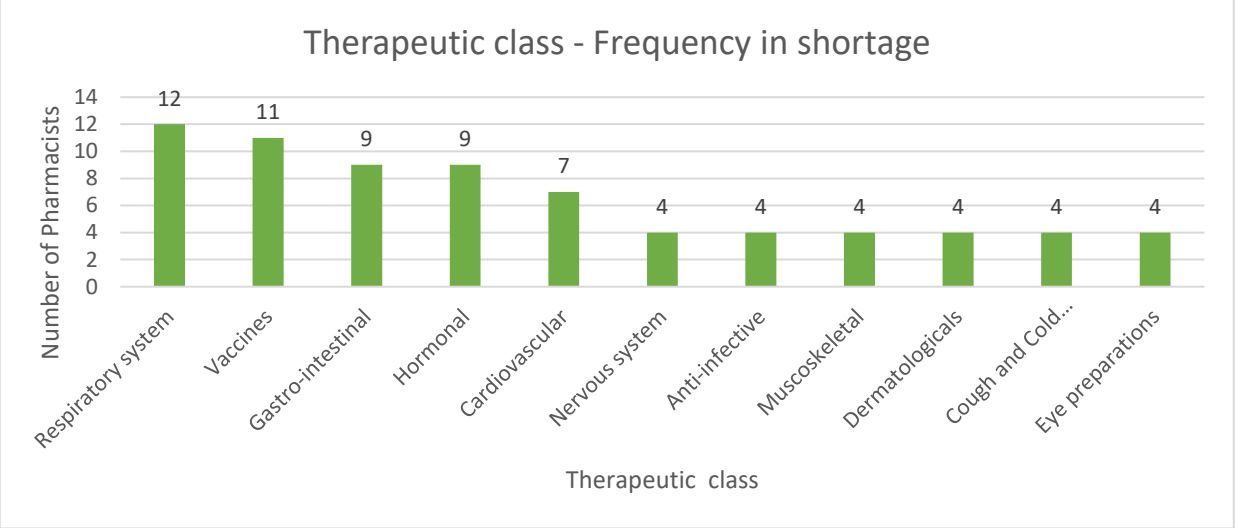

Figure 3.8 -Therapeutic classes experienced to be in shortages by pharmacists

When asked which solution was offered to the patient in case of medicine shortage through a multiple-choice question where respondents could tick more than one answer, 20 pharmacists offered substitution of the medicine in shortage was with an alternative, 18 pharmacists referred patient to doctor/prescriber, 2 answered provision of a lower dose and 12 pharmacists referred the patient to another pharmacy. It was noted that no pharmacist answered that patient was advised that missing or skipping a dose is necessary as a solution in case of medicine shortage. Most pharmacists (n=35) answered in the positive when asked whether there was any collaboration with the doctor/ prescriber when medicine required for patient treatment was in shortage. When asked about impact on patient when medicine was in shortage through use of a multiple-choice questionnaire where respondents could tick more than one answer, 8 reported sub-optimal treatment, 9 reported increase in expense to patient, 20 stated that medicine shortage caused distress and inconvenience, 7 reported cancellation of care, 15 reported delays in care, 2 reported medication error and 1 reported greater toxicity to patient. Figure 3.9 shows a summary of impact of medicine shortages on patient care identified through the research.

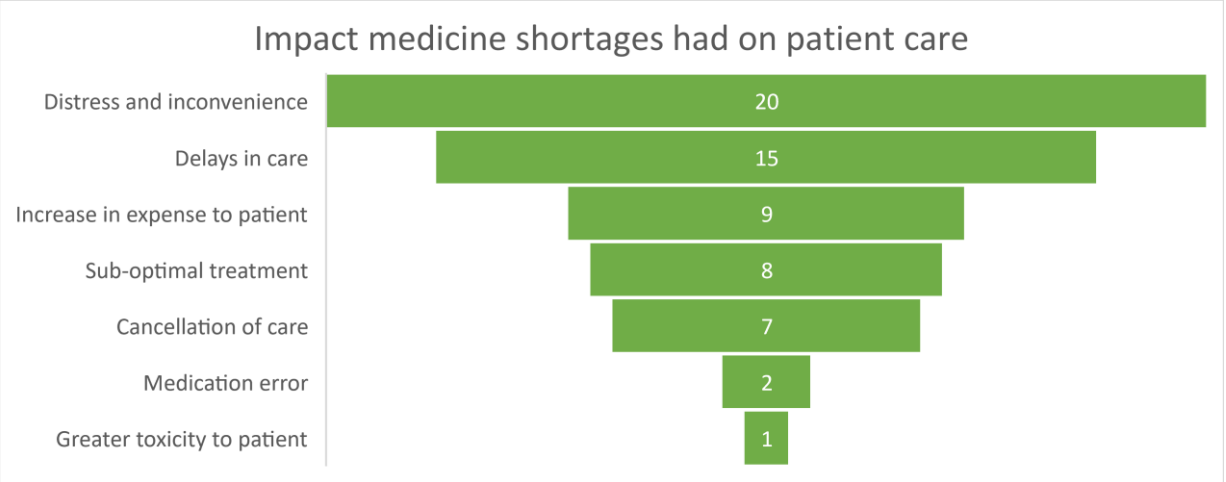

Figure 3.9- Impact medicine shortages had on patient care

Pharmacists were asked what type of impact medicine shortages present in community pharmacy had on them. Nineteen pharmacists stated that there was an increased workload to identify alternative product, 18 pharmacists stated that increased time was spent to mitigate shortages, 12 pharmacists stated that reduced patient/ pharmacists trust was experienced and 8 pharmacists stated that financial loss occurred due to the invested time mitigating shortages.

When the pharmacists were asked to list medicines which they experienced to be in shortage in the last 5 years from their community pharmacy, unrelated to medicines obtained through the POYC scheme, the following medications in table 3.4 were mentioned.

When asked whether shortages were present for medicines procured under the POYC scheme, 44 pharmacists answered in the affirmative and 6 pharmacists stated no. When asked whether communication with POYC was satisfactory, 33 pharmacists answered in the positive whereas 11 pharmacists answered in the negative.

Table 3.4- Medicines reported by pharmacists to be in shortage from community pharmacy

Medicines reported to be in shortage				
Solupred®	Diazepam 5mg tablets	Diacol®	Feminax®	Brufen Sachets®
Foradil®	Ditropan®	Maalox suspension®	Gavsicon Syrup® and Tablets®	Klaricid®

When asked about their experience with POYC when mitigating the medicine shortage through multiple-choice question where more than one answer could be chosen, 13 pharmacists stated that medicine shortage was remedied through urgent order, 8 pharmacists stated that no remedy or feedback was given on when medicine will be back in stock and 2 pharmacists stated that POYC was not reachable. When the pharmacists were asked to list medicines which they experienced to be in shortage in the last 5 years from the POYC scheme the following medications in table 3.5 were mentioned.

Table 3.5- Medicines reported by pharmacists to be in shortage from POYC

Medicines reported to be in shortage				
Omeprazole capsules	Amlodipine 5mg tablets	Warfarin all doses	Metformin 500mg tablets	Betamethasone cream
Mesalazine 400mg tablets	Atomoxetine tablets all doses	Methylphenidate 18mg, 36mg tablets	Rosuvastatin and Simvastatin	Morphine 10mg tablets
Levothyroxine 50mcg tablets	Paroxetine 20mg tablets	Hydrocortisone 10mg tablets	Etanercept injection	Travoprost eye drops

3.2 Study 2 results

A database was developed to gather the information collected from retrospective Article 20 exemptions. The database consisted of forty-four sections. Some of which where country of source of medicine, conditions of exemption, reasons for requesting exemption, reasons for rejection, considerations, status of application, therapeutic class, pharmaceutical formulation, average clock stops, average time taken to grant Article 20 exemption.

Following the development of a database to capture and standardize data relating to Article 20 exemption applications received between October 2020 to April 2022, qualitative and quantitative analysis was carried out to generate the following trends observed.

The number of applications received between October 2020 to April 2022 were 661. From the applications received 636 were approved and 25 applications were rejected. Figure 3.10 describes the amount of applications approved as a total from received.

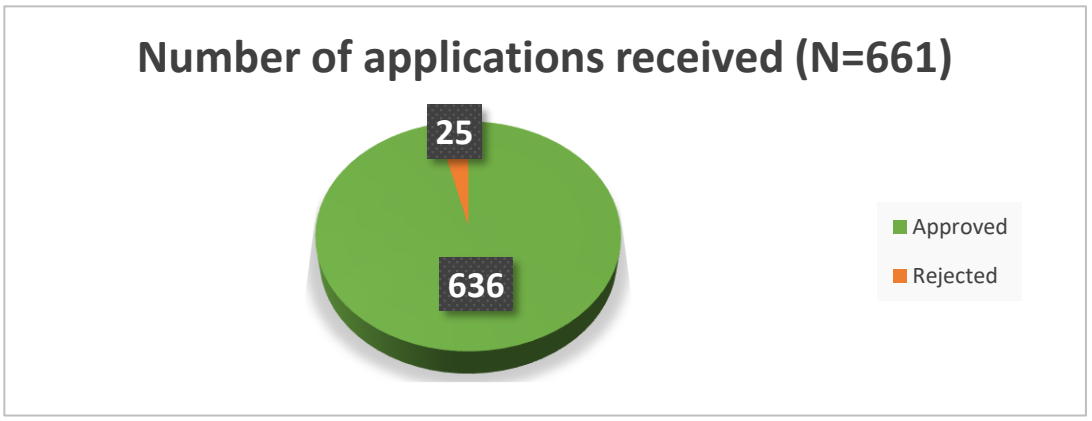

Figure 3.10-Article 20 applications received between October 2020 to April 2022

The highest number of applications approved were in March 2022 with 98 applications approved, the second highest was the subsequent month of April 2022 with 75 applications approved. The number of applications approved per month during the 19-month study period are presented in Figure 3.11.

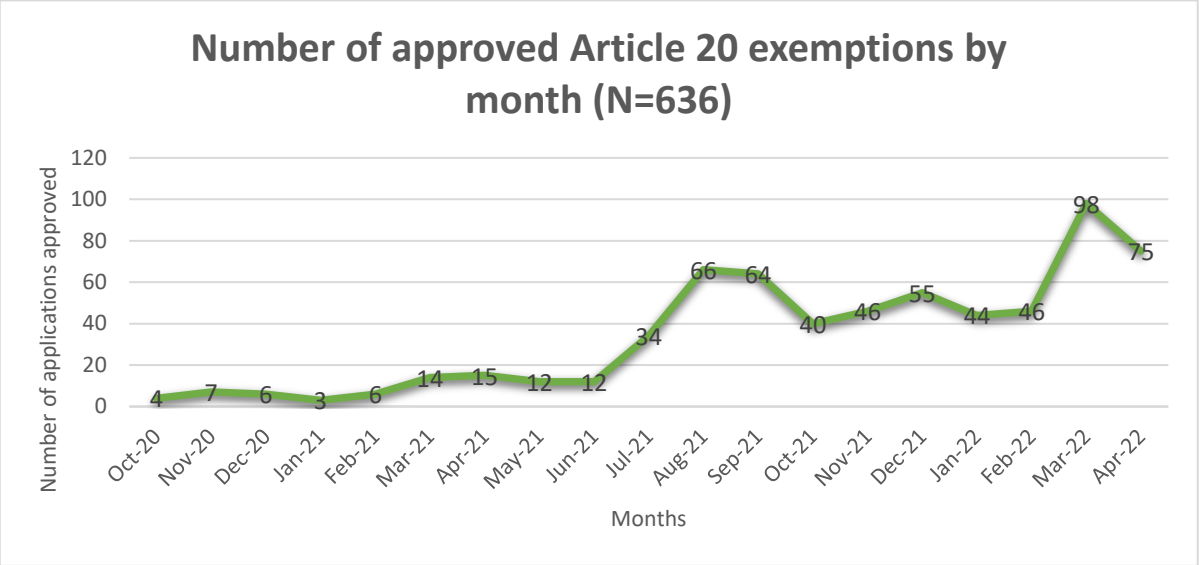

Figure 3.11- Number of approved Article 20 applications per month

From 661 applications received. 25 applications were rejected. Reasons for rejections include: 1) registered alternative is available (n=15) 2) product already registered (n=7) and 3) product should go through named patient route (n=3). Figure 3.12 summarises the number of applications received which were rejected or approved by month.

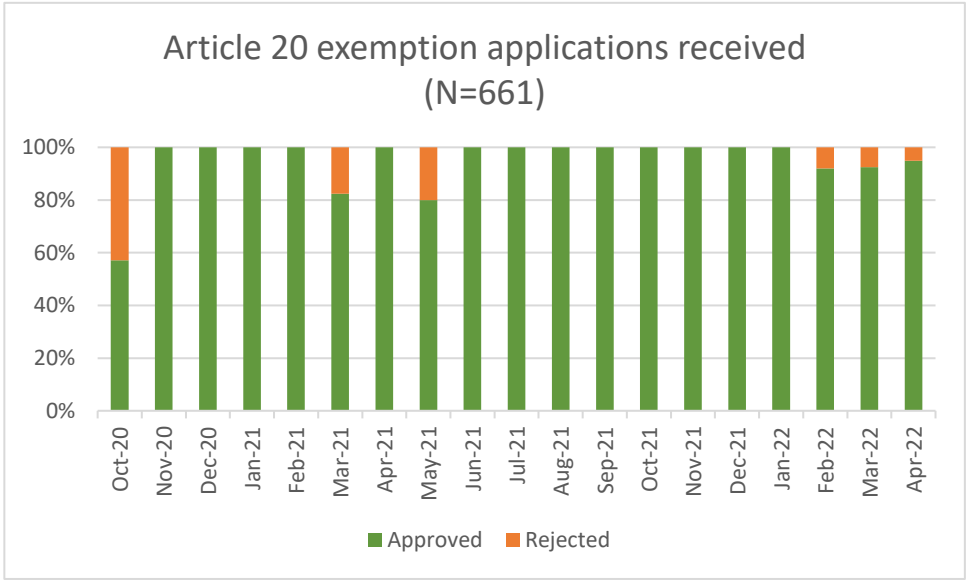

Figure 3.12-Number of received applications per month

Article 20 exemption applications can be approved for products sourced from different countries the most common country source is the United Kingdom (n=437). Figure 3.13 summarizes the country of source of approved applications.

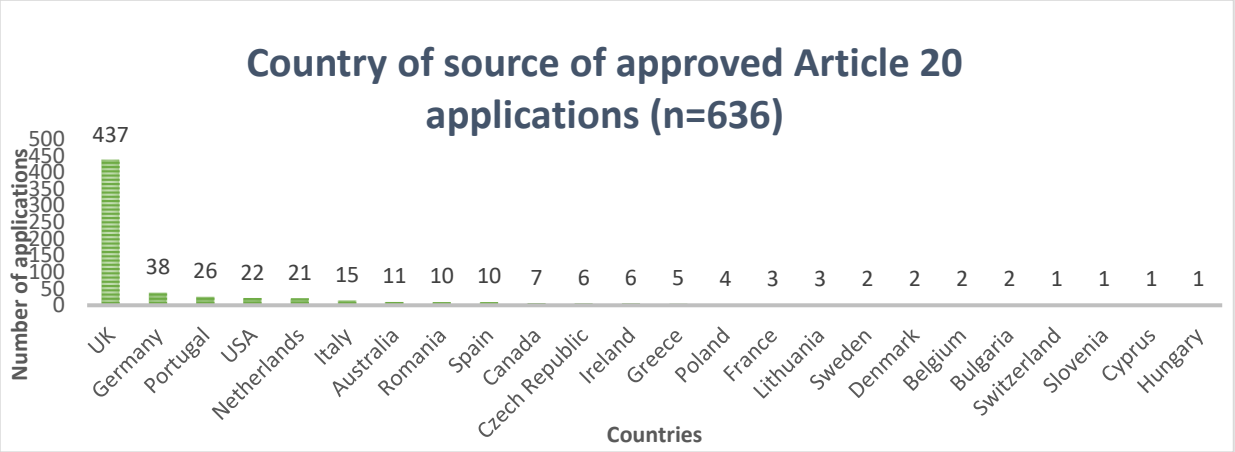

Figure 3.13- Country of source of approved Article 20 applications between October 2020 to April 2022

Reason for requesting an exemption refers to the public health justification provided by the applicant in the application. Reasons given for requesting an exemption include interim supply as new tender is in progress (n=247), international shortage (n=37), late delivery by supplier (n=75), product not available within the EU according to quotes (n=219), entity exceeded forecasted demand (n=14), item is required urgently (n=22), increase in consumption (n=35), interim measure until product is registered (n=7) and no registered offer received (n=10). It is to be noted that some applications contained more than one reason for requesting a exemption. Figure 3.14 depicts a summary of reasons for requesting a exemption:

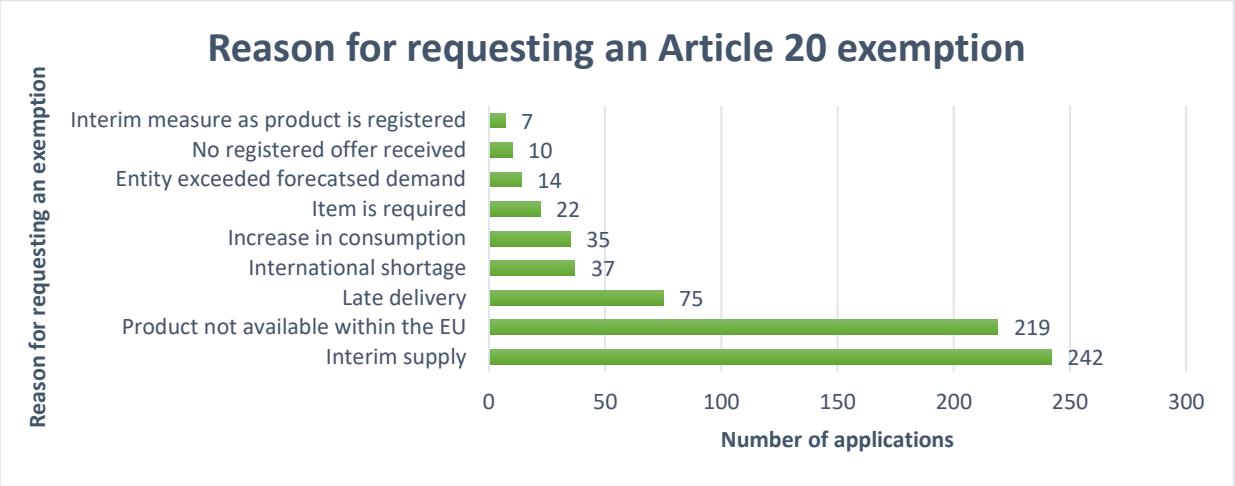

Figure 3.14- Reason for requesting an Article 20 exemption

Various medicines were approved under Article 20 exemption. The most common pharmaceutical formulation that was approved under Article 20 exemption was solution for injection/ infusion with 265 applications being approved for this formulation. The second most common formulation was tablets with 207 applications being approved. Figure 3.15 depicts the breakdown of approved Article 20 exemptions according to pharmaceutical formulation.

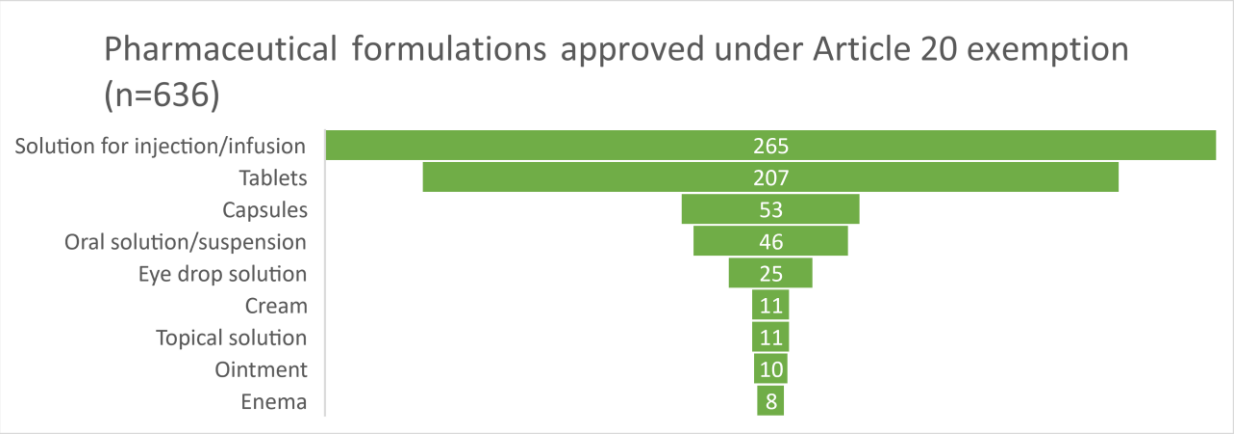

Figure 3.15-Pharmaceutical formulations approved under Article 20

The most common therapeutic class that was approved under Article 20 exemption was antibacterial for systemic use with 85 applications for medicines classifying under this class being approved. The second most common class was antineoplastic agents with 76 applications being approved followed by psycholeptics with 49 applications being approved for the class. Figure 3.16 depicts the breakdown of most approved Article 20 exemptions according to therapeutic class.

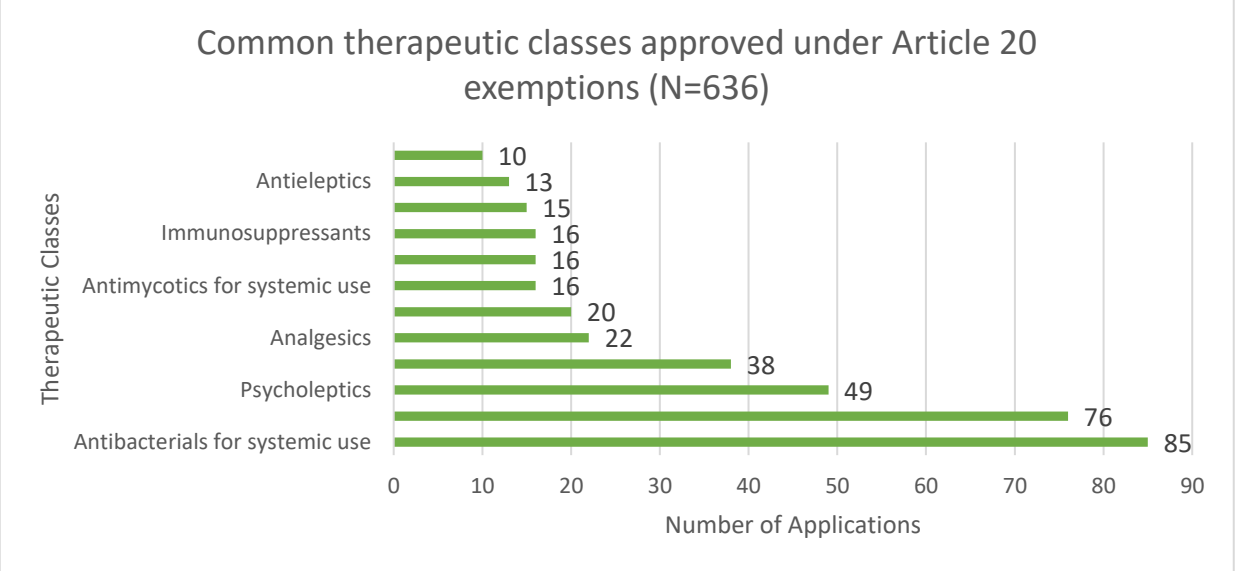

Figure 3.16- Most common therapeutic classes approved under Article 20 exemption

With all Article 20 exemption applications approved (n= 661) conditions were applied with the exemption. More than one condition can be applied for each exemption. Prioritize sourcing of products from the EU was the condition applied for 489 applications, register the product was applied for 171 of the applications and attach and English patient information leaflet (PIL) to each product was a condition for 164 exemptions.

The average time taken in days, to process an Article 20 exemption application was 14 days. The average amount of clock stops per application was 3 days. Clock stops refers to the amount of times processing of an Article 20 exemption application was halted due to missing information

or clarifications required from the applicant. Errors made by the applicant after Article 20 exemption was approved was seen in 14 of the 661 applications approved.

3.3 Study 3 results- The risk matrix

The results of study 3 of the research study consisted of categorization and classification of risk severity and risk probability of not granting an Article 20 exemption. The development of a 5x5 risk matrix which was piloted on retrospective Article 20 exemption applications. Identification of risk numbers to classify the matrix as low, medium and high-risk categories to further aid in the decision making when granting an Article 20 exemption was carried out through the focus group discussion. The risk matrix was validated after two rounds of discussion.

The risk matrix was developed through focus group discussion. The 5 x 5 risk matrix was developed on the WHO guidelines for quality risk management.[33] The focus group agreed and adopted a critical therapeutic class list. The following therapeutic classes were adopted as critical medicines: antibiotics, oncology medicines, blood products, vaccines, anticoagulants, parenteral medicines, diuretics, nutritional liquids, adrenaline auto-injectors, antihypertensives, anesthetics, radiopharmaceuticals, antiretroviral drugs and antineoplastic agents. Table 3.6 shows the risk matrix developed by the focus group developed.

[33] World Health Organization. WHO guidelines for quality risk management. 2013. [cited on 2022 May 25]. Available from URL: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf

Table 3.6- Risk matrix developed through focus group discussion

Risk Severity	Risk Probability				
	Almost Certain (5)	Likely (4)	Possible (3)	Unlikely (2)	Rare (1)
Catastrophic (5)	25	20	15	10	5
Hazardous (4)	20	16	12	8	4
Major (3)	15	12	9	6	3
Minor (2)	10	8	6	4	2
Negligible (1)	5	4	3	2	1

3.3.1 Risk Severity

Risk severity refers to the risk and impact on patient should an Article 20 exemption not be granted for a medicine. In order to further categorize risk severity, critical medicines were identified through focus group discussion. The focus group discussed the aspect of patient severity should a medicine be in shortage, after two rounds of deliberation the following classification was reached: catastrophic, hazardous, major, minor and negligible. Three aspects were considered for the classification, therapeutic use of the product, availability of alternatives and patient harm as a direct result of medicine being in shortage. Catastrophic referred to the application involving a critical medicine previously identified, with no alternatives present and can potentially cause patient death. Hazardous referred to the application involving a critical product which is medically necessary as it is a life supporting or life sustaining medicine for which there are no therapeutically equivalent alternatives and may cause irreversible patient harm. Major referred to the application involving a medicine which is used in the acute setting for short term or a medicine which is used in the long-term setting for a specific indication for which there are less than 3 therapeutic equivalent alternatives, shortage of a medicine within this category may involve reversible patient harm. Minor referred to an application involving a medicine which is required for short term, is a non-critical drug with 3 or more alternatives and shortage of this medicine would impact the patient more from a financially aspect than from a

clinical view. Negligible referred to the application containing a medicine which is not medically necessary would have no patient impact and more than 3 alternative medicines would be available.

During discussion in order to test out the accuracy, it was suggested to go through a retrospective analysis and apply the above criteria to pilot the classification. For catastrophic criteria the medicines aztreonam 1g and vancomycin were identified, for hazardous criteria the medicines adrenaline 1 in 10,000 injection and mivacurium solution for injection were identified, for major criteria the medicines labetalol solution for injection and propranolol solution for injection were identified, during round 2 of focus group discussion it was discussed and decided to move labetalol solution for injection to the hazardous category, for minor criteria the medicines hydrocortisone cream and paroxetine tablets were identified and for negligible the medicines aqueous cream, white soft paraffin and silver nitrate sticks were identified. The pilot was successful and was extended to all the Article 20 exemption applications approved between the research period. From the 636 applications approved, 296 applications were for medicines confirmed to be critical medicines through focus group discussion. From the 296 applications containing critical medicines, 256 were classified as catastrophic, 40 as hazardous, 297 as major, 36 as minor and 7 as negligible. Table 3.7 provides a summary of the criteria as agreed by the focus group discussion.

Table 3.7- Categories of the risk matrix as determined by the focus group

Risk Severity	Classification
Catastrophic	Critical medicine, no alternatives present and can potentially cause patient death
Hazardous	Critical medicine, life supporting or life sustaining medicine for which there are no therapeutically equivalent alternatives may cause irreversible patient harm.
Major	Medicine which is used in the acute setting for short term or a medicine which is used in the long-term setting for a specific indication for which there are less than 3 therapeutic equivalent alternatives, shortage of a medicine within this category may involve reversible patient harm.
Minor	Medicine which is required for short term, is a non-critical drug with 3 or more alternatives and shortage of this medicine would impact the patient more from a financially aspect than from a clinical aspect.
Negligible	Medicine which is not medically necessary would have no patient impact and more than 3 alternative medicines would be available.

3.3.2 Risk Probability

Risk probability refers to the chance of a consequence or severity occurring. The concept was first introduced to the focus group as a percentage chance of occurring, however through focus group discussion it was discussed that the probability in percentage would be difficult to quantify. The WHO guidelines for quality risk management were consulted and the suggested probability was adopted for this risk matrix.[34] Five risk probability categories were identified should Article 20 exemption not be granted leading to potential medicine shortage and lack of access to medicines with: almost certain defined as consequence seen to occur several times a year, likely

[34] World Health Organization. WHO guidelines for quality risk management. 2013. [cited on 2022 May 25]. Available from URL: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf

defined as consequence seen to occur more than once a year, possible defined as consequence seen to occur every 1-5 years, unlikely defined as consequence seen to occur every 5-10 years and rare defined as consequence seen to occur every 10-30 years.

3.3.2 Risk critical numbers

Risk critical numbers refer to the numbers or rather ranges identified through the focus group discussion to further classify the risk severity and risk probability identified in the risk matrix as low, medium and high risk. Through the focus group discussion, ranges for risk prioritization were identified (Table 3.8).

Table 3.8- Risk critical numbers

Risk Level: Probability x Severity	
Level	**Range**
Low	1-4
Medium	5-10
High	12-25

3.4 Summary of results

The results give light on impact of medicine shortages on the patient. It was observed from the perception of family doctors, pharmacists and patients that medicine shortages are a prevalent issue in the community pharmacy setting and impacts the patient from an economic, clinical and humanistic aspect. From the evaluation of the rationale of granting an Article 20 exemption a connection was observed between the medicines approved through the exemption and medicines in shortage from community setting namely; mesalazine tablets, paroxetine tablets, omeprazole tablets, metformin tablets, methylphenidate tablets, amlodipine tablets and betamethasone cream. Through the categorization of the risk related to the granting of an Article 20 exemption, patient impact arising from medicine shortages, can be prospectively mitigated.

Chapter Four

Discussion

4.1 Impact of medicine shortages

Medicine shortages are caused when disruptions in the supply chain affect patient accessibility to medicines. Economical, clinical and humanistic impacts on the patients, healthcare professionals and the national health systems result from lack of accessibility to medicines. Economic and clinical impacts of medicine shortages reported by Dill and Ahn, in 2014, Fox in 2014, Phuong et al in 2019 and Shukar et al in 2021 was experienced by participants in the study. A qualitative approach was adopted to assess the impact of medicines shortages on patients from the perspective of family doctors, pharmacists and patients. An aspect that was predominantly observed was the economic aspect when medicine was in shortage. To avoid treatment disruption a medicine alternative would be suggested by the pharmacist or doctor. Patients reported difference in price between medicine in shortage and alternative suggested to be from one Euro up to a difference of ten Euro. Medicine was reported to be in shortage from one month up to a year. In this study clinical impact was identified, by family doctors and pharmacists as; sub-optimal treatment, increased expense to patients, distress and inconvenience, cancellation of care, delays in treatment, medication error and increased toxicity to patients similarly reported by Becker et al, 2013; Mclaughlin et al, 2013; Dill and Ahn, 2014; Fox et al, 2014; Alsheikh et al, 2016; Mclaughlin et al, 2017; Rinaldi et al, 2017; Schwartzberg et al, 2017; Walker et al, 2017; Dave et al, 2018; Phuong et al, 2019, Shukar et al, 2021. From a humanistic impact it was observed that medicine shortage mitigation strategies lead to increased workload to identify alternative products, increased time mitigating medicine shortages, and reduced patient/pharmacist trust as also reported by Hedman, 2016; Rinaldi et al, 2017; Walker et al, 2017; Phuong et al, 2019; Shukar et al, 2021. Medicines reported to be in shortage from the POYC scheme were granted an Article 20 exemption to enhance accessibility to medicines and avoid disruption in patient treatment.

Applications approved were for products predominately sourced from the United Kingdom. This study highlighted the aspect where Malta is still dependent on sourcing products from the United Kingdom post-Brexit similarly discussed by Farrugia in 2018. When generating trends from retrospective analysis of Article 20 exemption applications, antibacterials for systemic use followed by antineoplastic agents were the most prominent therapeutic classes for which an exemption was granted. These therapeutic classes form part of the critical therapeutic class list agreed upon during the focus group discussion in this study. Similarly as observed by Miljković et al in 2020, different European countries identified antibacterials for systemic use and antineoplastic agents as critical if in shortage and require an immediate risk assessment.

From the 636 Article 20 exemption applications approved, 296 were for critical medicines. A Risk assessment is required to establish and categorise the risk of granting or not granting an Article 20 exemption application and prioritise applications. In order to minimize patient impact from medicine shortages, risk assessment during medicine shortage and prospective risk assessments are required as observed by Costelloe et al, 2015; Schwartzberg et al, 2017; Walker et al, 2017; Vogler and Fischer, 2020; Shukar et al, 2021. The risk tool developed through the focus group discussion is an innovative tool applicable to the current medicine shortage situation in order to effectively enhance current operations and mitigate potential medicine shortages. The tool is based on three aspects; clinical application of the medicine, alternatives present and patient impact should the medicine be in shortage. The clinical application of the medicine makes reference to the criticality of the therapeutic class as observed by Turbucz et al (2022) and Miljković et al in 2020. The different levels of impact of medicine shortages were similarly discussed by the European Association of Hospital Pharmacists in 2019 and Poulsen et al in 2021. During the focus group discussion, the shortcomings and issues of a failure mode and effect analysis were raised by the focus group members. The limitations of a risk matrix is the inability to accurately depict the probability especially in prospective research and how critical risk

numbers do not depict the impact the medicine shortage would have on the patient. In the applicable case of having a catastrophic event with a rare probability of occurring the number denoted is 5 but at the same time the same number is given for a medicine which has no patient impact but probability of occurring is almost certain. This is a limitation with risk matrices which is the reason a risk matrix cannot be interpretated on its own as discussed by Poulsen et al in 2021. The risk prioritization tool is an essential as a first step to develop an innovative decision-tree framework based on risk versus benefit of granting an Article 20 exemption. The risks of granting an Article 20 exemption are also considered since safety, quality and efficacy of the product needs to be established on the limited data available at time of granting an exemption.

4.2 Strengths and Limitations of the research

Experience of patients, family doctors and patients when facing medicine shortages in community indicated a correlation between Article 20 exemption approved to the NHS and patient impact from medicine shortages. A strength of this study was that an innovative risk tool that may be further explored into a decision tree minimizing patient impact when medicine shortages are present was developed.

The limitations were that dissemination of the three questionnaires intended for family doctors, pharmacists and patients contained missing data that could not be recorded as a full response.

A limitation of this research was that the focus group was specifically selected and was overshadowed from a regulatory approach as opposed to more of a clinical approach being undertaken.

Shortages related to medicines were tackled throughout this research and medical devices were not included.

4.3 Recommendations

As a result of the research, it is recommended to implement the risk matrix tool into a decision framework to aid in the risk rationale of granting or not granting an Article 20 exemption. It is recommended to initiate more discussions between pharmaceutical stakeholders from industry, the Medicines Authority and clinicians to aid in mitigation strategies through notification systems and collaboration with the National Health Service.

It is recommended to extend the questionnaire to gain the experience of family doctors, pharmacists and patients to include experience with medicine shortages from hospital.

It is recommended to further analyse the trends and rationale seen when granting an Article 20 exemption after the European Commission derogation[35] which extended Article 126(a) authorization for products obtained from the United Kingdom under strict justified public health needs when the medicine is not available from any other European country.

4.4 Conclusion

Medicine shortages impact the patient, healthcare professionals and national health systems. The consequences experienced by patients when a medicine is in shortage are significant and patient's quality of life is impacted from a clinical and economic perspective and a proactive approach is required to mitigate such shortages. Studying the perception of healthcare professionals and

[35] European Commission (EC). Application of the Union's pharmaceutical acquis in markets historically dependent on medicines supply from or through parts of the United Kingdom other than Northern Ireland. 2021 [cited 2022 May 26]. Available from URL: https://ec.europa.eu/info/publications/application-unions-pharmaceutical-acquis-markets-historically-dependent-medicines-supply-or-through-parts-united-kingdom-other-northern-ireland_en

patients when experiencing medicine shortages at the community setting contributes to policy and decision making.

Since the United Kingdom left the EU several medicines have been reported in shortage with no EU alternatives. Malta has had to rely on Article 20 exemption to maintain medicines stock position and avoid out of stock of critical medicines. Studying the perception of patients, pharmacists and healthcare professionals when experiencing shortages in a community setting emphasised the necessity of further work required to mitigate shortages through collaboration with pharmaceutical stakeholders. The evaluation of the rationale and the generating of trends observed from Article 20 exemptions requests was used to predict shortages. Not granting an Article 20 exemption might have significant consequences on the patient. The research identified 636 medicines that would have been in shortage if an Article 20 exemption was not granted. A risk-based approach facilitated processing of Article 20 exemption applications by classifying according to impact on clinical patient health outcomes identified through risk critical numbers. The development of criteria to measure risk of not granting an Article 20 exemption provides a strong patient-centered foundation for robust decision making while processing Article 20 exemption applications by safeguarding accessibility to medicines in exceptional humanitarian scenarios.

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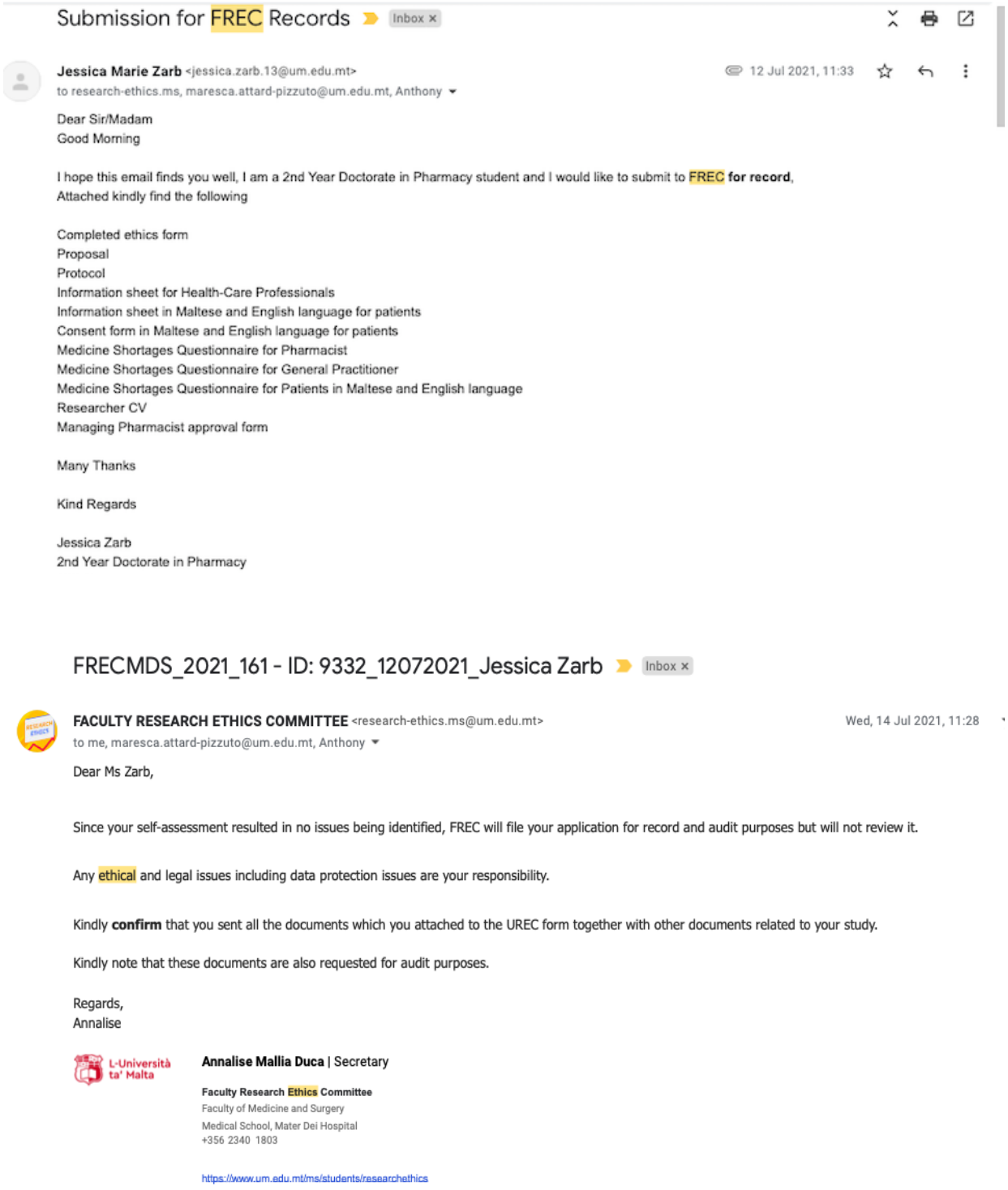
Appendices

Appendix 1
Faculty Research and Ethics Committee approval

Appendix 1: Faculty Research and Ethics Committee approval



Submission for FREC Records Inbox ×

Jessica Marie Zarb <jessica.zarb.13@um.edu.mt> 12 Jul 2021, 11:33
to research-ethics.ms, maresca.attard-pizzuto@um.edu.mt, Anthony

Dear Sir/Madam
Good Morning

I hope this email finds you well, I am a 2nd Year Doctorate in Pharmacy student and I would like to submit to FREC **for record**,
Attached kindly find the following

Completed ethics form
Proposal
Protocol
Information sheet for Health-Care Professionals
Information sheet in Maltese and English language for patients
Consent form in Maltese and English language for patients
Medicine Shortages Questionnaire for Pharmacist
Medicine Shortages Questionnaire for General Practitioner
Medicine Shortages Questionnaire for Patients in Maltese and English language
Researcher CV
Managing Pharmacist approval form

Many Thanks

Kind Regards

Jessica Zarb
2nd Year Doctorate in Pharmacy

FRECMDS_2021_161 - ID: 9332_12072021_Jessica Zarb Inbox ×

FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt> Wed, 14 Jul 2021, 11:28
to me, maresca.attard-pizzuto@um.edu.mt, Anthony

Dear Ms Zarb,

Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.

Any ethical and legal issues including data protection issues are your responsibility.

Kindly **confirm** that you sent all the documents which you attached to the UREC form together with other documents related to your study.

Kindly note that these documents are also requested for audit purposes.

Regards,
Annalise

L-Università ta' Malta

Annalise Mallia Duca | Secretary

Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1803

https://www.um.edu.mt/ms/students/researchethics

Jessica Marie Zarb <jessica.zarb.13@um.edu.mt> Wed, 14 Jul 2021, 11:45

to FACULTY, maresca.attard-pizzuto@um.edu.mt, Anthony

Dear Annalise,

Thank you for your email, I confirm that the applicable and requested documents as per UREC form have been attached

Many Thanks

Kind Regards

Jessica

•••

FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt> Wed, 14 Jul 2021, 11:56

to me, maresca.attard-pizzuto@um.edu.mt, Anthony

Dear Ms Zarb,

Thank you and good luck with your research!

•••

Reply Reply to all Forward

Screenshot

Appendix 2
Information sheet for patients in English and Maltese

Appendix 2: Information sheet for patients in English and Maltese

Information Sheet

Medicine Shortages

Dear Participant,

I am a Doctorate in Pharmacy student and I am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott.

The aim of this research is to study the perception of patients when facing medicine shortages through an anonymous and validated questionnaire titled `Medicine Shortages` available in both English and Maltese, which will take around 5 minutes to complete.

Your participation in this research will be kept strictly and completely confidential. Your identity and personal information will not be revealed in any publications, reports or presentations resulting from this research. Only information necessary for this study will be sought. Withdrawal or refusal to participate in this study shall carry no penalty. Data collected from this study will be anonymised.

Under the Data Protection Act, you have a right to access, rectify, and where applicable, ask for the data concerning you, to be erased.

Thank you in advance for your kind participation in this study

Kind Regards

Jessica Zarb

Email : jessica.zarb.13@um.edu.mt

Informazzjoni dwar l-istudju

Medicine Shortages

Jiena studenta tad- Dotorat fil-Farmacija u bhalissa qieghda nwettaq studju msejjah Medicine Shortages that is-supervizjoni tal- Professur Anthony Serracino Inglott.

L-ghan ta` din ir-ricerka hu li jkun studjat il-percezjoni ta pazjenti rigward nuqqas ta medicina b`uzu ta kwestjonarju validat li ghandu jiehu madwar 5 minuta biex jintela.

Il-parteipazzjoni tieghel f`din ir ricerka se tinzamm strettament u kompletament kunfidenzjali. L-identita u l-informazjoni personali tieghel mhux se jigu zvelati f`xi pubblikazzjoni, rapport jew prezentazzjonijiet li jirrizultaw munn din ir ricerka. L-infomrazzjoni li hija mehtiega ghal dan l-istudju biss ser tintalab titqassam. L-irtirara jew ir-rifjut ta` partecipazzjoni f`dan l-istudju m` ghandu l-ebda penali. Id-dejta migbura minn dan l-istudju se tkun anonimizzata

That l-Att dwar il-Protezzjoni u l-Privatezza tad-Data, ghandek id-dritt li taccessa, tirrettifika, u fejn applikabli titlob li d-dejta dwarek tigi mhassra

Inselli ghalik,

Jessica Zarb
Email : jessica.zarb.13@um.edu.mt

Appendix 3
Validation tool

Appendix 3: Validation tool

Dear

I am currently reading for Doctorate in Pharmacy course at the University of Malta. As part of course requirements I am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott.

The aim of this research is to study the experience of patients, family doctors and community pharmacists when facing medicine shortages through an anonymous questionnaire titled `Medicine Shortages`

I am humbly asking you to be a part of the panel for face and content validation of these questionnaires by using the attached rating tool.

Thank you for your time

Validation Tool

Occupation_____

Direction: This tool asks for your evaluation of the questionnaires to be used in the data gathering for the research titled `Medicine Shortages`. You are kindly requested to give your honest assessment using the criteria stated below. Please fill-in a different evaluation form for each questionnaire.

Scale	Interpretation
1	Strongly Agree
2	Agree
3	Neutral
4	Disagree
5	Strongly Disagree

Please check the appropriate box for your ratings

Criteria	**Scale**				
	1	**2**	**3**	**4**	**5**
Questions are of appropriate length					
Questions are unbiased and do not lead the participants to a response					
Questions are understandable					
The questionnaire is presented and organized in a logical matter					
Questions are adequate to address research question at hand					
Questions are not essential and need to be deleted (If yes state in remarks)					

Remarks_____

_____

_____

_____

Appendix 4
Information sheet for healthcare professionals

Appendix 4: Information sheet for healthcare professionals

Medicine Shortages

I am a Doctorate in Pharmacy student and I am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott.
The aim of this research is to study the experience of patients, family doctors and community pharmacists when facing medicine shortages through an anonymous and validated questionnaire titled `Medicine Shortages` available in both English and Maltese, which will take around 5 minutes to complete.
Your participation in this research will be kept strictly and completely confidential. Your identity and personal information will not be revealed in any publications, reports or presentations resulting from this research. Only information necessary for this study will be sought. Withdrawal or refusal to participate in this study shall carry no penalty. Data collected from this study will be anonymised.
Under the Data Protection Act, you have a right to access, rectify, and where applicable, ask for the data concerning you, to be erased.

Thank you in advance for your kind participation in this study
Kind Regards

Jessica Zarb
Mobile: 99778866
Email : jessica.zarb.13@um.edu.mt

Appendix 5
Questionnaire to assess the experience of family doctors with medicine shortages from community pharmacy

Appendix 5: Questionnaire to assess the experience of family doctors with medicine shortages from community pharmacy

MEDICINE SHORTAGES QUESTIONNAIRE- FAMILY DOCTOR

I am a 2nd Year Doctorate in Pharmacy student and I am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott. The aim of this research is to study the experience of patients, family doctors and community pharmacists when facing medicine shortages

Participant Number: _____

Section A: Personal Details

1. Age

☐ 24-34 ☐ 34-45 ☐ 46-55 ☐ 56+

2. Gender

☐ Male

☐ Female

☐ Other

3. Locality of Practice_____

4. Years of experience in community practice

☐ < 1 year

☐ >1 year

☐ 3 years

☐ >4 years

Section B: Experience with shortages on the private market

5. In the last 5 years, have you experienced medicine shortages in the private market?

   ☐ Yes

   ☐ No

6. How were you made aware of medicine in shortage?

   ☐ Community Pharmacist

   ☐ Patient

   ☐ Medical Representative

   ☐ News Article

   Other _____

7. Types of medicines most frequently in shortage (you may tick more than one)

   ☐ Cardiovascular Medications

   ☐ Vaccines

   ☐ Nervous System

   ☐ Respiratory System

   ☐ Gastro-intestinal medications

   ☐ Anti-infective medications for systematic use

   ☐ Systematic hormonal preparations

   ☐ Genito-urinary system and sex hormones

   ☐ Anti-neoplastic and immunomodulating agents

   ☐ Muscoskeletal system

   ☐ Dermatologicals

   ☐ Blood and Blood forming organs

   ☐ Anti-parasitic products, insecticides and repellents

Others _____

8. List medicines in shortage that have impacted your patient

Medicine Name	**Period of time it has affected patient in months**	**Month and Year of shortage (mm/yy)**

9. In case of presence of medicine shortages, which solution was offered to patient?

☐ Substitution of a medicine

☐ Advice that missing or skipping dose was necessary

☐ Provision of a lower dose

☐ Referred to another pharmacy

Other_____

10. Was collaboration with pharmacist present for medicines prescribed which were in shortage?

☐ Yes

☐ No

11. Type of impact medicine shortages had on patient care (you may tick more than one)

- [ ] Delays in Care
- [ ] Sub optimal treatment
- [ ] Cancellation of care
- [ ] Increase in expense to patient
- [ ] Medication error
- [ ] Greater Toxicity to patient
- [ ] Caused distress and inconvenience

Appendix 6: Questionnaire to assess the experience of pharmacists with medicine shortages from community pharmacy

MEDICINE SHORTAGES QUESTIONNAIRE- PHARMACIST

I am a 2nd Year Doctorate in Pharmacy student and I am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott. The aim of this research is to study the experience of patients, family doctors and community pharmacists when facing medicine shortages

Participant Number: _____

Section A: Personal Details

1. Age

☐ 23-30 ☐ 31-40 ☐ 41-50 ☐ 51-60 ☐ 61+

2. Gender

☐ Male

☐ Female

☐ Other

3. Locality of Practice_____

4. Years of experience in community practice

☐ < 2 year

☐ > 2year - ≥ 5 years

☐ > 6year - ≥ 10 years

☐ > 10 years

Section B: Experience with shortages (Tick whether shortage was present in community pharmacy or POYC, tick both columns if shortage present in both areas)

Question	POYC	Community Pharmacy
5. In the last 5 years, have you experienced medicine shortages? ☐ Yes ☐ No		
6. How were you made aware of medicines in shortage? ☐ Family Doctor ☐ Patient ☐ Medical Representative ☐ News Article ☐ Agent/wholesaler Other _____		
7. Types of medicines most frequently in shortage (you may tick more than one) ☐ Cardiovascular Medications ☐ Vaccines ☐ Nervous System ☐ Respiratory System ☐ Gastro-intestinal medications ☐ Anti-infective medications for systematic use ☐ Systematic hormonal preparations ☐ Genito-urinary system and sex hormones		

☐ Anti-neoplastic and immunomodulating agents ☐ Muscoskeletal system ☐ Dermatologicals ☐ Blood and Blood forming organs ☐ Anti-parasitic products, insecticides and repellents Others _____		

8. List medicines in shortage that have impacted your patients (Tick whether shortage was present in community pharmacy or POYC, tick both columns if shortage present in both areas)

Community Pharmacy	**POYC**	**Medicine Name**	**Period of time it has affected patient in months**	**Month and Year of shortage (mm/yy)**

Question	POYC	Community Pharmacy
9. In case of presence of medicine shortages, which solution was offered to patient? ☐ Substitution of a medicine ☐ Advice that missing or skipping dose was necessary ☐ Provision of a lower dose ☐ Patient referred to another pharmacy ☐ Patient referred back to doctor Other _____		
10. Was there collaboration with family doctor/ prescriber for medicines which were in shortage? ☐ Yes ☐ No		
11. What type of impact medicine shortages had on patient care? (you may tick more than one) ☐ Delays in care ☐ Sub optimal treatment ☐ Cancellation of care ☐ Increase in expense to patient ☐ Medication error ☐ Greater toxicity to patient ☐ Caused distress and inconvenience Other _____		

12. Type of impact medicine shortages had on pharmacist (you may tick more than one) ☐ Reduced patient/pharmacist trust ☐ Increased time spent to mitigate shortages ☐ Financial loss due to time invested in mitigating shortages ☐ Increased workload to identify alternative product ☐ Reduced professional satisfaction		

Section C: Experience with shortages through the POYC scheme

13. Was communication with POYC satisfactory?

☐ Yes

☐ No

14. Tick which best suits your experience with POYC

☐ Medicine shortage was remedied through an urgent order

☐ No remedy nor feedback given on when medicine will be back in stock

☐ POYC was not reachable

Appendix 7
Questionnaire to assess the experience of patients with medicine shortages from community pharmacy in English and Maltese language

Appendix 7: Questionnaire to assess the experience of patients with medicine shortages from community pharmacy in English and Maltese language

MEDICINE SHORTAGES QUESTIONNAIRE- PATIENTS

I am Jessica Zarb, a 2nd Year Doctorate in Pharmacy student and am currently conducting a study titled `Medicine Shortages` under the supervision of Professor Anthony Serracino Inglott. The aim of this research is to study the experience of patients, family doctors and community pharmacists when facing medicine shortages.

Participant Number: _____

Section A: Demographic Details

1. Age

☐ 18-30 ☐ 31-40 ☐ 41-50 ☐ 51-60 ☐ 61+

2. Gender

☐ Male

☐ Female

☐ Other

3. Highest level of education achieved

☐ Primary

☐ Secondary

☐ Post-secondary

☐ Tertiary

4. Locality of Residence _____

Section B: Experience with shortages (Tick whether shortage was experienced in the pharmacy when buying medicines or when collecting medications through POYC, tick both columns if shortage present in both areas)

Question	Community Pharmacy	POYC
5. In the last 5 years, have you experienced medicine shortages? ☐ Yes ☐ No		
6. Solution offered by pharmacist ☐ Substitution of a medicine ☐ Advised that missing or skipping dose was necessary ☐ Referred to doctor/prescriber ☐ Referred to another pharmacy ☐ Option to buy medicine from pharmacy		

7. List medicines in shortage that have impacted you **(**Tick whether shortage was experienced in the pharmacy when buying medicines or when collecting medications through POYC, tick both columns if shortage present in both areas)

Community Pharmacy	POYC	Medicine Name	Period of time it has affected patient in months	Month and Year of shortage (mm/yy)

Question	POYC	Community Pharmacy
8. Was the medicine shortage solved to your satisfaction? ☐ Yes ☐ No		
9. Reasons why it was not solved to your satisfaction ☐ The medicine suggested as substitute caused unwanted side effects ☐ The medicine suggested as substitute was higher in price ☐ No alternative was available ☐ Alternative medicine was not as effective as medicine in shortage		
10. In case of medicine shortage, approximately what was difference in price between medicine in shortage and alternative medicine suggested? ☐ less than 1 euro ☐ €1-€5 ☐ More than €5 ☐ More than €10		
11. For how long did you have to buy the alternative medication? ☐ 1-3 months ☐ >3 months ☐ >5 months ☐ >1 year		

Comments:

KWESTJONARJU DWAR PROVVISTA BAXXA TA’ MEDIĊINA - PAZJENTI

Jiena Jessica Zarb, studenta tat-Tieni Sena fid-Dottorat fil-Farmaċija u bħalissa qed immexxi studju intitolat "Provvista Baxxa ta’ Mediċina" taħt is-superviżjoni tal-Professur Anthony Serracino Inglott. L-għan ta' din ir-riċerka huwa li tiġi studjata l-esperjenza ta' pazjenti, tobba tal-familja u spiżjara tal-komunità meta jaffaċċjaw provvista baxxa ta' mediċina.

Numru tal-Parteċipant: _____

Taqsima A: Dettalji Demografiċi

1. Età

☐ 18-30 ☐ 31-40 ☐ 41-50 ☐ 51-60 ☐ 61+

2. Sess

☐ Raġel

☐ Mara

☐ Oħrajn

3. L-ogħla livell ta' edukazzjoni miksub

☐ Primarju

☐ Sekondarju

☐ Post-sekondarju

☐ Terzjarju

4. Lokalità ta' Residenza _____

Taqsima B: Esperjenza b'provvisti baxxi (Immarka jekk in-nuqqas kienx esperjenzat fl-ispiżerija meta tixtri mediċini jew meta tiġbor il-mediċini permezz tal-POYC, immarka ż-żewġ kolonni jekk ikun hemm nuqqas fiż-żewġ oqsma)

Mistoqsija	Spiżerija tal-Komunità	POYC
5. F'dawn l-aħħar 5 snin, għaddejt minn esperjenza ta' provvista baxxa ta' mediċina? ☐ Iva ☐ Le		
6. Soluzzjoni offruta mill-ispiżjar: ☐ Sostituzzjoni ta' mediċina ☐ Avżat/a li doża nieqsa jew maqbuża kienet meħtieġa ☐ Irreferut lura għand it-tabib / riċettur ☐ Irreferut għand spiżerija oħra ☐ Għażla li tixtri mediċina mill-ispiżerija		

7. Elenka l-mediċini nieqsa li kellhom impatt fuqek (Immarka jekk in-nuqqas kienx esperjenzat fl-ispiżerija meta tixtri mediċini jew meta tiġbor il-mediċini permezz tal-POYC, immarka ż-żewġ kolonni jekk in-nuqqas ikun preżenti fiż-żewġ oqsma)

Spiżerija tal-Komunità	POYC	Isem tal-Mediċina	Perjodu ta' żmien (xhur) li affettwa lill-pazjent	Xahar u Sena ta' nuqqas (xx/ss)

Mistoqsija	Spiżerija tal-Komunità	POYC
8. In-nuqqas tal-mediċina ġie solvut għas-sodisfazzjon tiegħek? ☐ Iva ☐ Le		
9. (Jekk le) Raġunijiet għaliex ma ġietx solvuta għas-sodisfazzjon tiegħek ☐ Il-mediċina ssuġġerita bħala sostitut ikkawżat effetti sekondarji mhux mixtieqa ☐ Il-mediċina ssuġġerita bħala sostitut kienet ogħla fil-prezz ☐ L-ebda alternattiva ma kienet disponibbli ☐ Il-mediċina alternattiva ma kinitx effettiva daqs il-mediċina nieqsa		
10. Fil-każ ta' nuqqas ta' mediċina, bejn wieħed u ieħor x'kienet id-differenza fil-prezz bejn il-mediċina nieqsa u l-mediċina alternattiva ssuġġerita? ☐ Inqas minn Ewro ☐ Bejn €1- €5 ☐ Iktar minn €5 ☐ Iktar minn €10		

11. Għal kemm żmien kellek tixtri l-medikazzjoni alternattiva? ☐ 1 - 3 xhur ☐ >3 xhur ☐ >5 xhur ☐ > sena		

Kummenti:

_____

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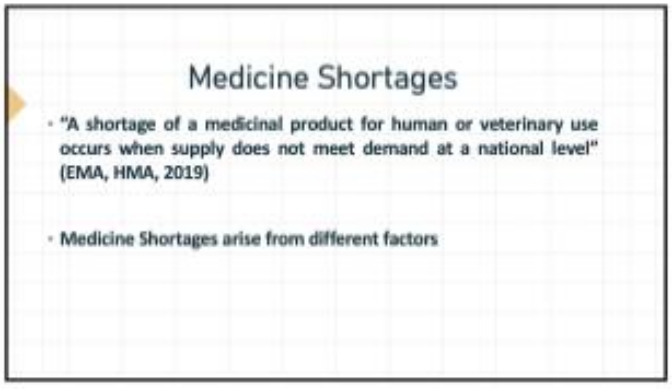
_____

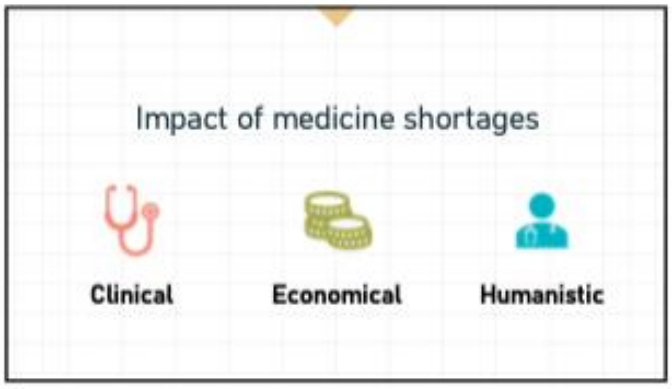
Appendix 8
Focus Group presentation- I

Appendix 8: Focus group presentation- I

1



2



3

Mitigation Strategies

- **Creation of a national critical medicine list**
- **Identification of alternative drugs**
- **Prospective risk assessments**
- **Temporary importation of unlicensed products**

4

Article 20

- Article 20 in accordance with the Medicines Act Chapter 458 is an emergency exemption which is granted for a medicinal product not currently holding a marketing authorisation under strict exceptional cases.

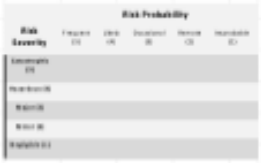
5

- Failure Mode and Effects Analysis is a tool that identifies all possible failures and prioritises failures according to the severity of consequences arising from the failure.

6

Risk Matrix

- Risk Matrix is made up of Risk Severity and Risk Probability
- Risk Severity relates to risk and impact to patient.
- Risk Probability relates to how probably the consequences of not granting an Article 20 are likely to occur



7

Risk Critical Number

- Risk Critical Number is Severity X Probability
- Derived from the Risk Matrix
- Allows for classification of Risk in three categories: Low, Medium, High

Risk Level: Probability X Severity	
Level	Range
Low	
Medium	
High	

8

Aim of the Focus Group

- The aim of the focus group is to determine the categories in a Risk Matrix (Risk Probability X Risk Severity) relating to associated risks and impact on patient when recommending the granting or not granting of an Article 20 exemption to the Licensing Authority.

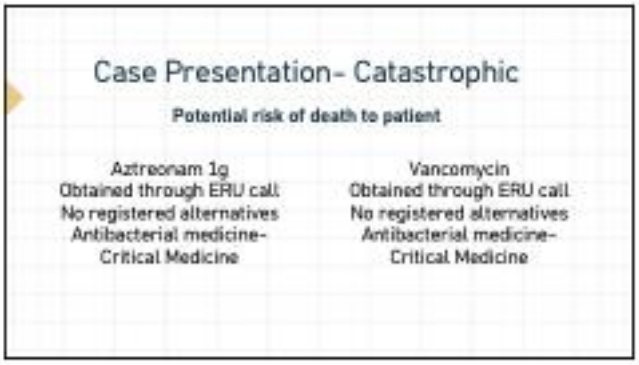
9

10

Appendix 9
Focus group presentation-II

Appendix 9: Focus group presentation- II

1



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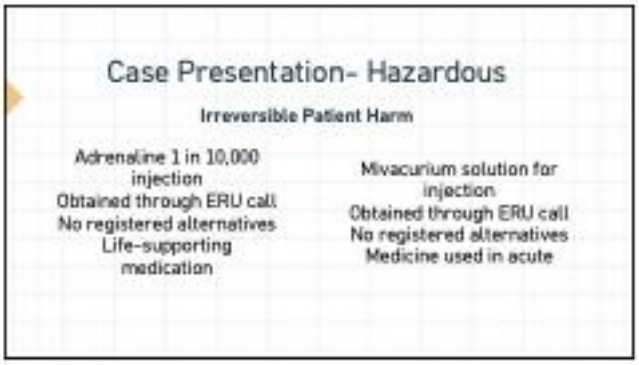

3

Case Presentation- Major

Reversible Patient Harm

Labetalol
Obtained through ERU call
Medicine used for specific cases
Less than 3 alternatives present

Propranolol solution for injection
Obtained through ERU call
Medicine used for specific cases
Less than 3 alternatives present

4

Case Presentation- Minor

Patient Quality of Life Affected

Hydrocortisone Cream
Required for short term use
3 or more alternatives

Paroxetine
Obtained through ERU call
3 or more alternatives present

5

Case Presentation- Negligible

No to little patient impact

No patient impact. No shortage of product medically necessary
Aqueous cream, White Soft Paraffin, Silver Nitrate Sticks

6

7