Post-Brexit and Availability of Medicines

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Abstract

The United Kingdom (UK) officially left the European Union (EU) single market and customs union on December 2020. Since the UK is now considered a third country of the EU, unavailability of medicinal products from the UK across EU member states is expected. Small member states such as Malta have sourced their medicine supply from the UK. The unavailability of or insufficient supply of medicines represents a significant obstacle to patients' access to medicines. The aim of the study was to understand how Brexit has affected medicine availability in Malta. The objectives were: to identify which medicines are not available post-Brexit and to recognize experiences of different pharmaceutical sectors involved in the supply chain when it comes to medicine availability after Brexit.

The study was divided into 2 phases. Phase 1 was a review of databases which includes the Government Formulary List (GFL) and the Malta Medicines Authority (MMA) Marketing Authorization database. The status of the marketing authorizations of medicines in the GFL, as well as, the status of medicines in the MA database from the MMA website were identified. Applications to make medicines with identified Withdrawn and Invalidated MA from the UK available were checked. Phase 2 consisted of individual semi-structured interviews to determine the stakeholders' perspectives and experiences post-Brexit.

A total of 542 Marketing Authorizations (MA) with the MA Holder based in the UK were withdrawn and a total of 544 MA were Invalidated MA from the UK since they no longer met EU legislation requirements. Twenty-nine stakeholders participated in the interviews. Challenges related to Brexit reported by the stakeholders (N = 29) were: *Financial costs* (n = 26); *Brexit is an unprecedented event* (n = 23); and *Public's attitude*

towards medicines (n = 21). The interviewees unanimously stated (n = 29) that although the unavailability of medicines is caused by different events happening concurrently such as the Covid-19 pandemic, escalating conflicts between nations and reports of Active Pharmaceutical Ingredient manufacturing concerns, Brexit had an impact on Malta's medicine availability.

Medicine unavailability has impacts on economic, clinical, and humanistic levels especially relevant to member states with small pharmaceutical markets such as Malta where unavailability of medicines is a problem. Sourcing out medicines from different EU countries would allow greater availability of medicines. Measures established, primarily regulatory measures, such the use of Article 20 of the Medicines Act; address the availability problems. Not only do the measures provide short-term solutions and help prevent medicines shortages, but also lay down the ground work in the long run.

Keywords: Brexit, Availability, Medicines, Marketing Authorization, Malta

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List of Abbreviations

AI	Active Ingredient
API	Active Pharmaceutical Ingredients
ATC	Anatomical Therapeutic Chemical
Brexit	British exit
COVID-19	Coronavirus Disease 2019
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EML	Essential Medicines List
EU	European Union
GFL	Government Formulary List
GMP	Good Manufacturing Process
HMA	Heads of Medicines Agencies
MA	Marketing Authorization
MAHs	Marketing Authorization Holders
MIAU	Medicines Intelligence and Access Unit
MMA	Malta Medicines Authority
UK	United Kingdom
WHO	World Health Organization

Chapter One

Introduction

1.1 Medicine Availability

The World Health Organization (WHO) defines medicine availability as "*the degree to which a medicine is present at distribution points in a defined area for the population living in that area at the moment of need.*"[1] Bidgeli et al., (2012) stated that availability of medicines *"represents supply and includes manufacturing, forecasting, procurement, distribution and delivery functions."*

1.1.1 Availability as a dimension of Access

The WHO equitable access to essential medicines framework presents four dimensions: Essential medicine use, Fair prices, Pharmacoeconomics, and Availability of medicines;[2] to help formulate pharmaceutical policies and coordinate efforts to improve medicine access. The four essential dimensions must exist for national health systems to guarantee access to medications.[3]

A taxonomic definition of access was introduced by Penchansky and Thomas (1981) where "access" is presented as a broad concept that encapsulates a set of more specific dimensions illustrating the link between the health care

[1] World Health Organization. WHO guideline on ensuring balanced national policies for access and safe use of controlled medicines [Internet]. World Health Organization. [cited 18 November 2022]. Available from: https://www.who.int/news/item/22-12-2020-who-guideline-on-ensuring-balanced-national-policies-for-access-and-safe-use-of-controlled-medicines

[2] World Health Organization. Equitable access to essential medicines: a framework for collective action. World Health Organization. 2004 [cited 11 April 2023]. Available from: https://apps.who.int/iris/handle/10665/68571

[3] Muscat C. Drug Intelligence and Access to Medicine [Master's Thesis]. Malta. University of Malta; 2020.

system and the patient. The dimensions are acceptability, accessibility, accommodation, affordability and availability. Saurman (2016) added a sixth dimension of access – awareness. Each dimension is interrelated and fundamental to one another in terms of enabling or impeding access to medications.

Availability pertains to the adequacy of the supply of health care providers, facilities and specialized programs and services. It refers to the relationship between the type and volume of existing services and resources to the types and volumes of client's needs (Penchansky & Thomas, 1981).

Medicine access is a fundamental human right (Rafi et al., 2021). The unavailability of or insufficient supply of necessary medications may represent a significant obstacle to patients' access to medications (Shambira et al., 2021).

1.2 Pharmaceutical Supply Chain

The pharmaceutical supply chain includes planning, execution and management of all operations involving the movement of materials and information, from the acquisition of raw materials through the final delivery of the drug to the patient.[4] Components of the pharmaceutical supply chain have a direct impact on how consistent the drug supply is. The ability of

[4] Pradolin D. What is the Pharmaceutical Supply Chain? [Internet]. Qualifyze. 2023 [cited 20 March 2023]. Available from: https://www.qualifyze.com/what-is-the-pharmaceutical-supply-chain/

involved stakeholders to manage disruptions is essential to patient care.

Different stakeholders are involved in pharmaceutical supply chains, from Active Pharmaceutical Ingredient (API) producers to retail pharmacies. Medication shortages are frequently brought on by disruptions within the supply chain (Tucker & Daskin, 2022).

1.3 Medicine Shortage

Medication shortages appear to be a worsening global problem. In recent years, medication shortages have become more common in Member States of the European Union (EU) (De Weerdt et al., 2016).

The ability of national healthcare systems to provide continuity of care has been significantly impacted by the increase of medicine shortages in European countries. Studies by Beck et al., (2019) and Acosta et al., (2019) has identified four main categories that can be linked to the description of shortage situations: the market, supply chain management, manufacturing and political issues. These categories are interrelated and affect the availability of safe and effective medications.

One of the seminal cross-country reports on medicine shortages in Europe made the suggestion that the causes of shortages may be divided into unpredictable and predictable problems as listed in Table 1.1. This report included an in-depth analysis of situation in France, Greece, Poland, Spain,

and the United Kingdom (UK) (Bochenek et al., 2018).

Table 1.1: Predictable and Unpredictable Reasons for Shortages

Adapted from: Evaluation of medicines shortages in Europe - EAEPC [Internet]. [cited 20 March 2023] Available from: https://www.eaepc.org/images/An_evaluation_of_medicines_shortages_in_Europe_.pdf

Unpredictable	Predictable
Natural Disasters	Product discontinuation
Manufacturing problems	Industry consolidation
Raw Material Shortages	Limited manufacturing capacity
Non-compliance with regulatory standards	Just-in-time inventories
Packaging shortages	Rationing / Quotas
Unexpected demand	Deliberate shortages to manipulate price
Epidemics	Market shifts
Parallel distribution	Launch of a new competitor, new formulation, or patent expiry
Competitive issues	
Foreign exchange effect	
Sovereign issues (financial crisis, debt, default)	

Shukar et al., (2021) classified causes of drug shortages into three main issues as shown in Figure 1.1. Demand-, supply-, or regulatory-related issues, unforeseen and complex, result in shortages. Medications may not be available due to both supply-related e.g., production, distribution,

logistics, and regulatory challenges; and demand-related factors e.g., drug demand fluctuations, tendering, parallel market, price and reimbursement schemes. A crucial element in regulatory concerns is the lack of a standardized definition of drug shortage.

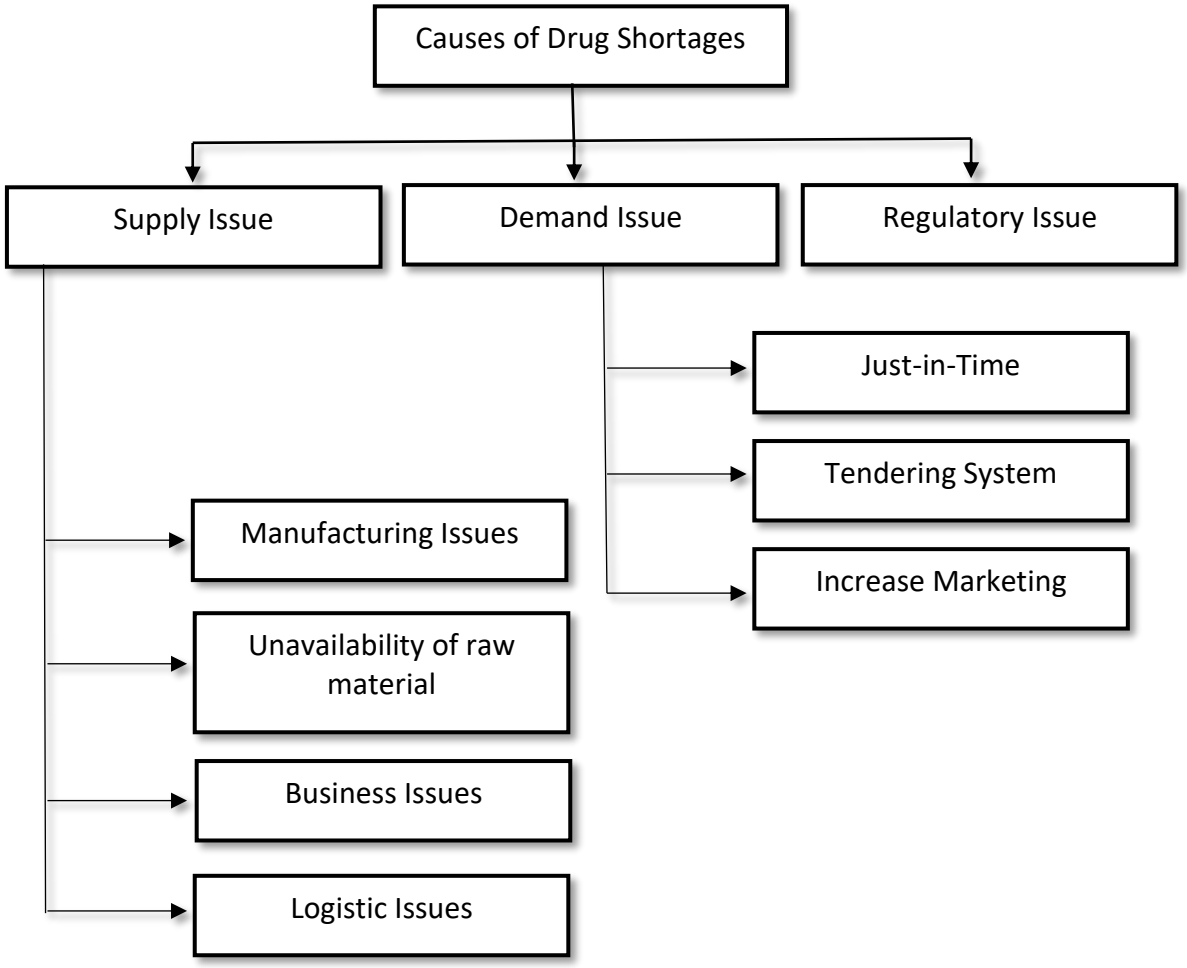

Figure 1.1: Causes of Drug Shortages

Adapted from: Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, et al. Drug shortage: Causes, impact, and Mitigation Strategies. Frontiers in Pharmacology. 2021;12:693426.

The first standardized "shortage" definition in the European Economic Area (EEA) was published in 2019 by the European Medicines Agency (EMA) and

Heads of Medicines Agencies (HMA).[5] The proposed definition was only applicable to Marketing Authorization Holders (MAHs) and regulatory authorities, and it represents fostering coordination and communication among European pharmaceutical stakeholders, regulators and experts working in the various National Healthcare Systems to increase resistance to shortages (Musazzi et al., 2020).

Geopolitical incidences, such as Brexit and the COVID-19 pandemic, can have a significant impact on the stability of the pharmaceutical supply chain and patients' access to treatment (Musazzi et al., 2020). The COVID-19 pandemic hampered the supply chain for drugs and medical equipment, reducing their availability and affecting patient care (Abed et al., 2022).

Shortages or other problems related to the availability of medicines create challenges that cannot be associated to just one cause.[6] Manufacturers, wholesalers, and pharmacies share a responsibility to ensure the availability of pharmaceuticals.[7]

[5] European Medicines Agency. Guidance for MAHS on the detection and notification of shortages [Internet]. European Medicines Agency. [cited 18 November 2022]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf

[6] European Medicines Agency. Availability of medicines [Internet]. European Medicines Agency. 2022 [cited 14 December 2022]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines

[7] Heads of Medicines Agency. Availability of medicines for human use - heads of medicines agencies [Internet]. [cited 20 December 2022]. Available from: https://www.hma.eu/human-medicines/availability-of-medicines.html

1.4 Essential Medicines

The WHO published its first essential drugs list in 1977 in response to the need for improved access to pharmaceuticals. This list evolved into the essential medicines list (EML), which is currently in its 18th iteration (Masters et al., 2014). The EML aids in establishing the idea that some medications are more beneficial than others and should be readily available to the population (Laing et al., 2003).

According to the WHO, essential medicines are those that address the population's top healthcare needs. They are chosen with consideration for their potential impact on public health, evidence of their efficacy and safety, and comparative cost-effectiveness.[8] Many countries embrace the strategy of developing national EMLs to manage their respective disease loads in cost-effective ways (Masters et al., 2014).

1.4.1 Drug Formularies

A drug formulary is a list of medicines that is continuously updated and backed by current evidence-based medicine and opinions of health care workers in the diagnosis, treatment, and preservation of health. Drug formularies should promote appropriate resource management without limiting or negatively delaying medically necessary care. Every prescriber,

[8] World Health Organization. Who model list of essential medicines - 22nd list, 2021 [Internet]. World Health Organization; [cited 20 December 2022]. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

pharmacist and patient are impacted by drug formularies.[9] The formulary's main goal is to promote the safest, most efficient, and cost-effective medicines available.[10]

1.5 Marketing Authorization

The EU medicine regulatory system is a network of regulatory authorities from the member countries of the EEA, the European Commission (EC) and the EMA.[11] Cooperation between all involved agencies ensures that medicine regulation across the EU is efficient and effective. Experts collaborate from all over the EEA to share their expertise and exchange information in the regulation of medicines ensuring that patients have access to safe medicines. The European system offers different authorization routes: the centralized procedure, the decentralized procedure and the mutual-recognition procedure. Rules and requirements applicable to pharmaceuticals in the EU are the same, irrespective of the authorization route for a medicine.[12]

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[9] The Kennedy Forum. A consumer guide to drug formularies: Understanding the fundamentals of behavioural health medications. 2017 [cited 11 April 2023] Available from: URL: https://www.paritytrack.org/issue_briefs/a-consumer-guide-to-drug-formularies-understanding-thefundamentals-of-behavioral-health-medications/

[10] Academy of Managed Care Pharmacy. Formulary Management. AMCP.org. [cited 11 April 2023]. Available from: https://www.amcp.org/about/managed-care-pharmacy-101/concepts-managed-care-pharmacy/formulary-management

[11] European Medicines Agency. European regulatory system. [cited 16 October 2022]. Available from: https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf

[12] Life Science Industry Coalition. UK Exiting from EU. [cited 24 October 2022]. Available from: https://www.medicinesforeurope.com/wp-content/uploads/2017/12/UK-Exiting-from-EU_LIFE-Science-industry-coalition_POSITION-PAPER-FINAL.pdf

The needs of the pharmaceutical markets in large member states are different than those of smaller member states (Said et al., 2018, Di Giorgio et al., 2019). MAHs might not find it profitable to expand their production facilities and offer their pharmaceutical products in minor European nations. In this situation, the National Regulatory Authorities may undertake regulatory procedures to hasten the release of the marketing authorization e.g., Art. 126a of Directive 2001/83/EC; for the availability of medications on the national market. Parallel trading may be a viable option to ensure medicine availability (Musazzi et al., 2020). A small English-speaking nation like Malta, in addition to the granting of National Marketing Authorizations, ensures its medicine supply mostly through Art. 126a authorizations with parallel importation supplementing the remaining needs.[13] The use of Art. 126a enables MAHs of authorized products in other English-speaking EU member states (such as the UK and Ireland) to have simple access to the Maltese market.[14] Garel and Pascal (2018) noted that changes to the existing arrangements may have consequences on medicine access across all European member states.

[13] Farrugia C. Pharma World Magazine. 2018 [cited 24 October 2022]. Available from: https://www.pharmaworldmagazine.com/preparations-for-impact-of-brexit-pharmaceutical-supply-chain-malta/

[14] European Medicines Agency. European authorities working to avoid shortages of medicines due to ... [Internet]. [cited 14 November 2022]. Available from: https://www.ema.europa.eu/en/documents/other/european-authorities-working-avoid-shortages-medicines-due-brexit-questions-answers_en.pdf

1.6 National Pharmaceutical Regulatory Authority in Malta

In Malta, as established in the Medicines Act of 2003, the Licensing Authority is the responsible national entity for the authorization of medicine in the Maltese Market.[15] The Medicines Act of 2003 and the Medicines (Marketing Authorization) Regulations Act allows marketing authorization to be granted nationally.[16]

The Malta Medicines Authority (MMA), provides the Licensing Authority the pertinent information needed to provide the marketing authorization to medicines by being the designated regulatory body that processes marketing authorization applications.[17,18]

Through defined national and European procedures, the Licensing Directorate handles all requests for product pre-authorization and post-authorization activities. This encompasses all product-related licenses and authorizations, including those that are granted, withdrawn, modified, revoked, or suspended. MIAU's responsibilities include managing a proactive and focused strategy, introducing and facilitating the implementation of best practices, and improving

[15] Medicines Act. Malta, 2003. [cited 11 February 2023]. Available from: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1

[16] Medicines (Marketing Authorisation) Regulations, 2007. [cited 11 February 2023] Available from: http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=11272&l=1

[17] Medicines Act. Malta, 2003. [cited 11 February 2023]. Available from: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1

[18] Malta Medicines Authority. Directorates and Units [Internet]. Medicines authority [cited 11 February 2023]. Available from: http://www.medicinesauthority.gov.mt/directoratesunits

access to and intelligence about medications.[19] The MIAU is also responsible for Article 20 applications.

The MMA uses three marketing authorization pathways: the centralized procedure, the decentralized procedure that subscribes to the mutual recognition procedure, and the national procedure.[20]

1.6.1 Centralized Procedure

An application for a marketing authorization must be submitted to the EMA in order to receive a community authorization through the Centralized procedure. On the basis of a single marketing authorization, this permits the marketing-authorization holder to market the medicine and make it available to patients and healthcare professionals across the EU. Since their MA is valid throughout the EU/EEA, products authorized by the central system may be automatically marketed in Malta. Before a medicine is made available to patients in a particular EU country, decisions on pricing and reimbursement are made at the national levels within the context of the country's national health system. [21,22]

[19] Malta Medicines Authority. Directorates and Units [Internet]. Medicines authority. [cited 22 December 2022]. Available from: https://medicinesauthority.gov.mt/directoratesunits?l=1

[20] Malta Medicines Authority. Registration [Internet]. Medicines authority [cited 11 February 2023]. Available from: http://medicinesauthority.gov.mt/registration

[21] European Medicines Agency. Authorisation of medicines [Internet]. European Medicines Agency. 2021 [cited 20 March 2023]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#centralised-authorisation-procedure-section

[22]Malta Medicines Authority. Centralised Procedure [Internet]. Medicines authority. [cited 20 March 2023]. Available from: https://medicinesauthority.gov.mt/centralisedprocedure

1.6.2 Decentralized Procedure or Mutual Recognition Procedure

To obtain marketing authorization in multiple EU Member States for a medicine that falls outside the purview of the centralized system, the applicant may choose one of the following paths: Mutual recognition procedure that allows marketing authorizations issued in one EU Member State to be recognized in other EU countries; or Decentralization procedure which allows for simultaneous authorization of a drug in many EU Member States even though it has not yet received EU authorization.[23]

1.6.3 National Procedure

The national procedure involves two types of authorization according to the articles of Medicines (Marketing Authorization) Regulations and Directives that they operate in. The first authorization procedure is in accordance with regulation 4(1), in accordance with articles 8 and 10 of Directive 2001/83/EC. The second authorization procedure grants authorization with regulation 4(2), in accordance with article 126(a) of Directive 2001/83/EC.[24]

1.7 Article 20 of the Medicines Act of 2003

Article 20 of the Medicines Act of 2003 states the provisions that in exceptional circumstances, if the marketing authorization for a medicinal

[23] European Medicines Agency. Authorisation of medicines [Internet]. European Medicines Agency. 2021 [cited 20 March 2023]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#centralised-authorisation-procedure-section

[24] Malta Medicines Authority. Nationals [Internet]. Medicines authority [cited 11 February 2023]. Available from: http://medicinesauthority.gov.mt/nationals

product is not yet available following the other routes of authorization, it will allow the use of the medicinal product in Malta subject to conditions.[25] The use of Article 20, in line with the commitment of providing access to medicines to the Maltese public, is a precautionary regulatory measure taken by stakeholders involved as a proactive action to ensure that medicines are made available as the demand and situation dictates.

Other countries in the EU have clauses in their Laws and Directives that are similar in function to Article 20 of the Malta Medicines Act of 2003. Some examples of these are: Hungary, as per their Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products, allows provisional marketing authorization for patient care interests.[26] Prescribers in Ireland have access to unauthorized medicines for their patients as addressed in the Medicinal Products (Control of Placing on the Market) Regulations, 2007.[27] Finland's national responsible authority grants a special permit to medicinal products in conditional circumstances.[28]

[25] Bonanno PV, Flores G. Seven years of EU pharmaceutical regulation in Malta. WHO Drug Information 2011;25(4):343-353.

[26] Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products, 2005. Hungary. [Accessed 14 November 2022]. Available from: https://net.jogtar.hu/jogszabaly?docid=a0500095.tv&dbnum=62&getdoc=1

[27] Health Products Regulatory Authority. Access to Medicine Prior to Authorization; Supply of unauthorized medicines in accordance with the specifications of a practitioner for use by his individual patients. Ireland. [Accessed 14 November 2022]. Available from: http://www.hpra.ie/homepage/medicines/regulatory-information/medicines-authorisation/access-to-medicines-prior-to-authorisation

[28] Pharmaceutical Regulation Pursuant to the Law on Medicinal Products, 1987. Finland. [Accessed 14 November 2022]. Available from: https://finlex.fi/fi/laki/ajantasa/1987/19870693#V2

1.8 Article 126A of Directive 2001/83/EC

Article 126a of Directive 2001/83/EC states that: *"In the absence of a marketing authorization or of a pending application for a medicinal product authorized in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorize the placing on the market of the said medicinal product."* [29]

Products approved within the terms of Article 126a are subject to the same laws and regulations as any other route of authorization before they can be placed on the market. Applicants are requested to consider the other routes of authorization before using Article 126a as a last resort.[30]

1.9 United Kingdom leaving the European Union

On June 2016, a referendum was held wherein the majority of the UK voted to leave the EU. A transition period started on January 31, 2020 and ended in December 2020.[31] The transition period was created to give stakeholders time to get ready for the effects of the full implementation of Brexit. Trade

[29] Malta Medicines Authority. Authorization in line with Regulation 4(2) of the Medicines (Marketing Authorization) Regulations, in accordance with Article 126(A) of directive 2001/83/EC [Internet]. Medicines Authority. [cited 12 December 2022]. Available from: http://medicinesauthority.gov.mt/126a

[30] Zammit A. Developments in Article 126A Authorisations in Malta [Internet]. Pharma World. 2021 [cited 12 December 2022]. Available from: https://www.pharmaworldmagazine.com/malta-developments-in-article-126a-authorisations-in-malta/

[31] Walker N. Brexit timeline: events leading to the UK's exit from the European Union [Internet]. House of Commons Library. 2022 [cited 19 October 2022]. Available from: https://commonslibrary.parliament.uk/research-briefings/cbp-7960/

agreements between the UK and EU were still in force during the transition period. With the help of this agreement, trade in goods—including pharmaceuticals—between the EU and the UK was smooth. If pharmaceutical companies were still functioning in the UK at the time, the transition period gave them the opportunity to move their activities into an EU member state.[32] The EEA authorities have been aiding participants in the transition phase since May 2017, pressing them to make the required adjustments before Brexit was fully implemented. This strategy lessens the risk of compromising the supply of medications to EU member states.[33]

The UK officially left the EU single market and customs union on December 31, 2020 as the Brexit transition period came to an end. This political event had repercussions not only in the UK but also in other member states. Subject to the withdrawal agreement to other EU member states, EU laws that require each Member State to operate the same requirements regarding the authorizations and monitoring of medicines will no longer apply to the UK (Breckenridge et al., 2018). Changes to the movement of medicinal products were expected since the UK is now considered a third country by the EU.

[32] Ferolin P. The Derogations for Accessibility of Medicines from the UK [Master's Thesis]. Malta. University of Malta; 2020.

[33] European Medicines Agency [Internet]. European authorities working to avoid shortages of medicines due to Brexit. 2020 [cited 8 November 2022]. Available from: https://www.ema.europa.eu/en/documents/

1.10 Derogations issued post-Brexit

Proposals have been placed forward to mitigate the negative consequences of Brexit on access to medicines.[34] The EC published a number of derogations in the months following Brexit to help with challenges the competent national authorities encountered when trying to import medicines from the UK. These derogations are geared to assist the smaller markets of the EU, such as Malta, after the end of the transition period.[35]

Small member states such as Cyprus, Ireland and Malta have sourced a majority of their long term medicine supply from the UK.[36] As small member states have considerably smaller pharmaceutical markets, before Brexit, they could acquire a fraction of batch productions without commitment to the whole batch that would otherwise be produced explicitly for its small market size.[37] Being one of the member states that require medicine's packaging to be in the English language, Malta's medicine supply relies significantly on the UK due to the joint packaging.[38]

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[34] European Parliament. Access to medicinal products. 2021. [cited 19 October 2022]. Available from: https://www.europarl.europa.eu/RegData/etudes/STUD/2021/662910/IPOL_STU(2021)662910_EN.pdf

[35] Malta Medicines Authority. BREXIT - Regulatory Considerations [Internet]. 2022 [cited 16 October 2022]. Available from: https://medicinesauthority.gov.mt/brexit

[36] European Commission. Press corner. European Commission - European Commission. 2022 [cited 16 October 2022]. Available from: http://ec.europa.eu/commission/presscorner/detail/en/qanda_21_6912

[37] Galea Debono F. Popular medicines no longer available as Brexit takes its toll. Times of Malta. 2021 [cited 16 October 2022]. Available from: https://timesofmalta.com/articles/view/popular-medicines-no-longer- available-as-brexit-takes-its-toll.892324

[38] Anda B. Possible Consequences of Brexit on European Pharmaceutical Market. University of Latvia. [cited 16 October 2022]. Available from: https://dspace.lu.lv/dspace/bitstream/handle/7/54169/Batraga_A_Kite_M_ Duboviks_J_Salkovska_J_NC_2020.pdf?sequence=1

For a period of three years, Malta, Cyprus, and Ireland will benefit from exemptions under certain conditions, for example medicines will not have to undergo a repeat batch testing again if they have been initially tested in the UK.[39]

1.11 The COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) outbreak started on November 2019 and was declared as a global pandemic by WHO on March 11, 2020,[40] and placed a massive strain on health systems all over the world. The Covid-19 pandemic had an impact on the global economy, which included the pharmaceutical industry (Ayati et al., 2020).

1.11.1 Impact of Covid-19 on the Pharmaceutical Industry

In managing the pandemic, the challenges faced by the pharmaceutical industry were observed, including difficulty providing the need for protective equipment and diagnostic testing facilities. Due to the closure of facilities, particularly in China, where the majority of active pharmaceutical ingrediants are produced, the Covid-19 problem had a direct impact on the scarcity of medical supplies, supply chain uncertainty, logistics, and

[39] European Qualified Person Association. Brexit and Northern Ireland - what's new?. ECA Academy. 2022 [cited 23 January 2022]. Available from: https://www.gmp-compliance.org/gmp-news/brexit-and-northern-ireland-whats-new

[40] World Heal Organization. In: Coronavirus disease (COVID-19) outbreak situation. WHO. 2020 [cited 11 April 2023]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 23 April 2020.

transportation (Hamed et al., 2020). The worldwide shutdown has resulted in fewer imports and exports of pharmaceuticals. The majority of pharmaceutical manufacturing companies have turned their focus to the production of drugs and medical equipment intended to combat COVID-19 in their countries (Kretchy et al., 2021).

Protocols designed to stop the Covid-19 outbreak from spreading have limited the capacity to procure raw materials, manufacture and transport pharmaceuticals. In developing and underdeveloped nations without manufacturing capabilities, this presents a significant difficulty. A gap in the manufacturing of medications for other chronic diseases is created by prioritizing the production of pharmaceuticals and equipment targeted against Covid-19 (Hamed et al., 2020).

In a study conducted by Ayati et al., (2020), short-term and long-term impacts of the pandemic to the pharmaceutical industry were identified. Short term impacts included: research and development shifts; communication shifts toward tele-medicine; medicine shortages due to 1) induced Covid-19 treatment demands, 2) general induced demand and 3) supply shortages. Long-term impacts identified are: approval delays of non-Covid related products; shifts towards self-sufficiency; slow-down in the growth of the pharma industry; changes in consumption patterns; and ethical dilemmas.

The pandemic has demonstrated that having strong supply chains and constant access to medicines, so that health systems function as seamlessly as possible, is important. [41]

1.12 Rationale of the Study

Brexit is a geopolitical event that required amendments in existing policies and guidelines in the medicine supply chain. Responsible bodies had to adapt regulations to mitigate the consequences of the UK leaving the EU and ensure that medicine availability in the remaining member states is not heavily impacted. Granting of Marketing Authorizations (MA) is the first step for any medicinal product to be made available in the market. Reviewing the registered marketing authorizations in Malta would provide a picture on how Malta's medicine supply is moving towards a post-Brexit landscape. Understanding the stakeholders' experiences can help identify gaps and provide suggestions on mitigation strategies that can aid in ensuring medicine availability.

1.13 Aims and Objectives

The study aims to understand how Brexit has affected medicine availability in Malta. The objectives are:

- To identify which medicines are not available post-Brexit
- To recognize the experiences of the different pharmaceutical

[41] European Commission. Press corner [Internet]. European Commission - European Commission. [cited 20 December 2022]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_22_2385

sectors involved in the supply chain when it comes to medicine availability due to Brexit

Chapter Two

Methodology

2.1 Research Overview

The study was divided into 2 phases. Phase 1 was a review of databases which includes the Government Formulary List (GFL) and the Malta Medicines Authority (MMA) Marketing Authorization (MA) database. The status of the marketing authorizations of medicines in the GFL, as well as, the status of medicines in the MA database from the MMA website were identified. Availability of applications to make the medicines with identified Withdrawn MA from the UK was checked. Phase 2 is an individual semi-structured interviews to determine the stakeholders' perspectives and experiences post-Brexit.

2.2 Research Setting

The study was conducted at the MMA at the Licensing Department and the Medicines Intelligence and Access Unit (MIAU).

2.3 Research Design

Quantitative and qualitative data was collected in the review of databases, while qualitative information was gathered from a semi-structured interview with pharmaceutical stakeholders.

2.4 Ethics Application

The study was registered with the Faculty Research Ethics Committee (FREC) of the University of Malta Faculty of Medicine & Surgery (Appendix 1).

2.5 Phase 1 – Databases Review

The Marketing Authorization database was extracted from the MMA website on March 2023.

2.5.1 Review of Medicines in the Government Formulary List

The GFL consist of medicinal products, vitamins and food supplements. Medicines on the GFL were reviewed to identify whether all the medicines in the formulary have national authorized marketing authorizations.

Medicines on the GFL were sorted based on their ATC code and active ingredients belonging to either of the following group were excluded: Officially deleted Active Ingredient (AI), Availability of AI temporarily suspended due to problematic sourcing, Extemporaneous compounded AI, AI STOMA code (Instead of ATC codes the AI has STOMA indicated which refers to supplies for a stoma), AI with no ATC code.

The identified AI with no National Authorized MA were sorted into their Disease Category as stated in the GFL. From the identified AI with no National Authorized MA, the ones from the UK were identified. The MIAU was contacted to confirm if Article 20 was granted for AI with no National Authorized MA from the UK. Therapeutic substitutes available in the GFL were identified for those that were not granted exemptions on the basis of Article 20.

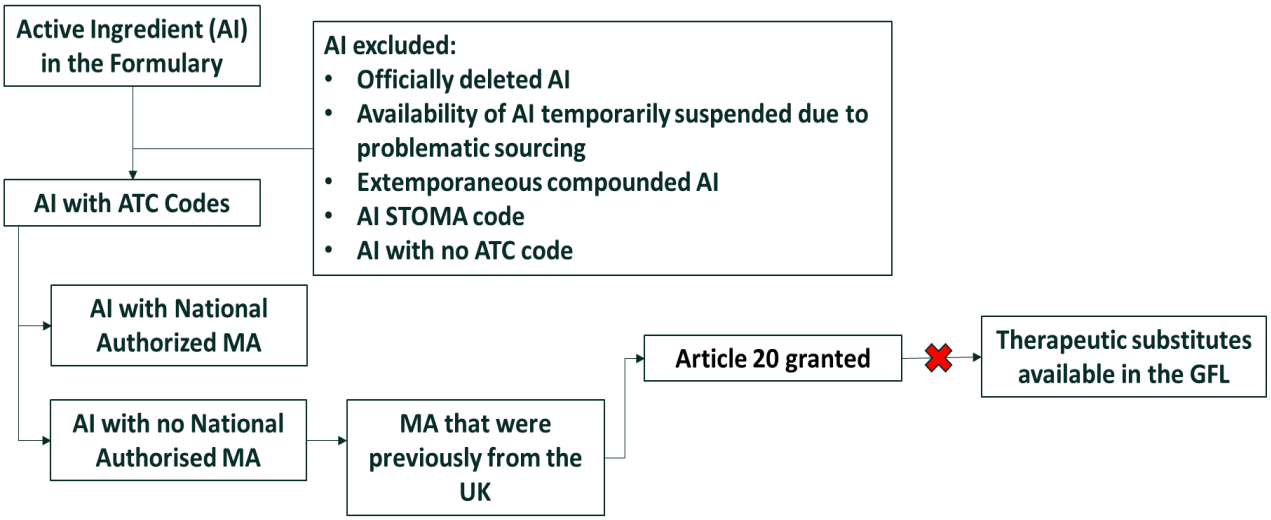

Figure 2.1: Summary of Phase 1.i: Government Formulary List Review

2.5.2 Review of Medicines in the Malta Medicines Authority Marketing Authorization Database with Withdrawn and Invalidated MA from the UK

Medicines with MA with the MA Holder based in the UK that were withdrawn by the companies and Invalidated MA from the UK that no longer met requirements in the EU legislation were identified.

Medicines with Withdrawn MA and Invalidated MA from the UK were reviewed with Authorized MA to check if new applications have been made to make the same medicines available in Malta. Medicines with no new identical Authorized MA were then reviewed to check if there were alternatives with Authorized MA available. Alternatives with Authorized MA available were considered if the Authorized MA was for a medicine that had the same active ingredient but with a different strength or dosage form. The MIAU was contacted to confirm if Article 20 was granted for AI with no alternative Authorized MA. Therapeutic substitutes were identified for those that were not granted exemptions on the basis of Article 20.

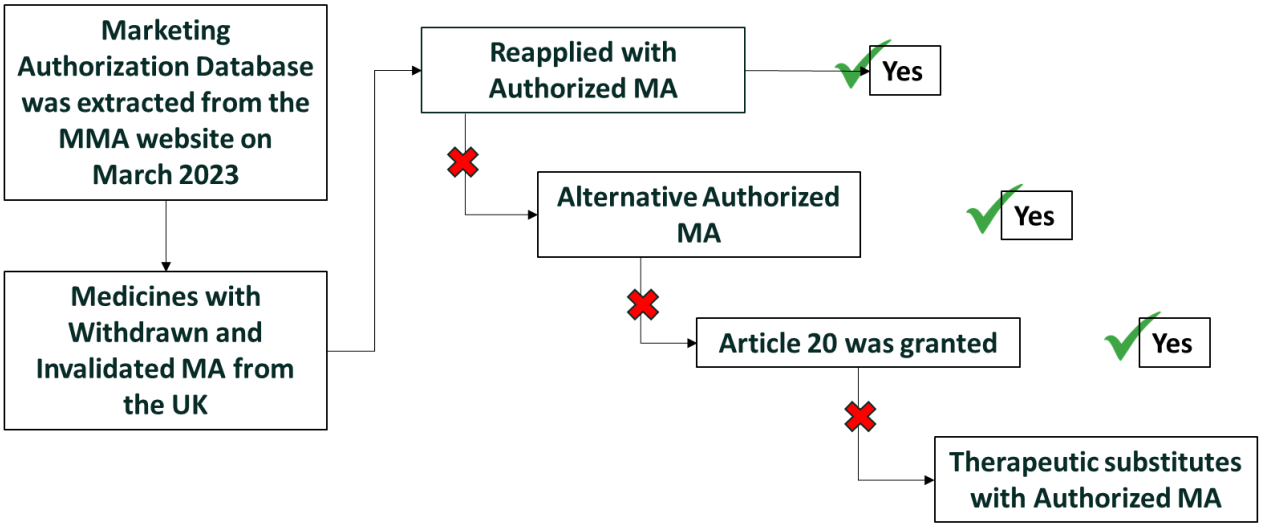

Figure 2.2: Summary of Phase 1.ii: Malta Medicines Authority Marketing Authorization Database Review

2.6 Phase 2 – Pharmaceutical Sector Stakeholder Interviews

Data was collected by means of semi-structured interviews with participants based on a purposive sample of stakeholders. Individual semi-structured interviews were carried out to determine the stakeholders' views and experiences post-Brexit. An email communication was sent out to request participation of interested stakeholders in regulatory, hospital, wholesalers, and community. The interview involved a facilitated discussion, aided by four questions answerable with a Likert scale (Appendix 2), on what challenges the interviewees have encountered and how the over-all experience has defined the current state of medicine availability in Malta.

Data was analyzed using thematic analysis. The data gathered was sorted into specific themes derived from recurring ideas and key words used by the participants in their answers.

Chapter Three

Results

3.1 Phase 1 – Results of Review of Databases

3.1.1 Review of the Government Formulary List

There were 1,306 products listed in the formulary which was reduced to 1,260 products after exclusion as summarized on Figure 3.1. The ATC codes of the Active Ingredients (AI) listed in the formulary was used to match them with the ATC codes of authorized national marketing authorizations. There are 1,072 AI with authorized marketing authorization and 188 AI with no authorized marketing authorization.

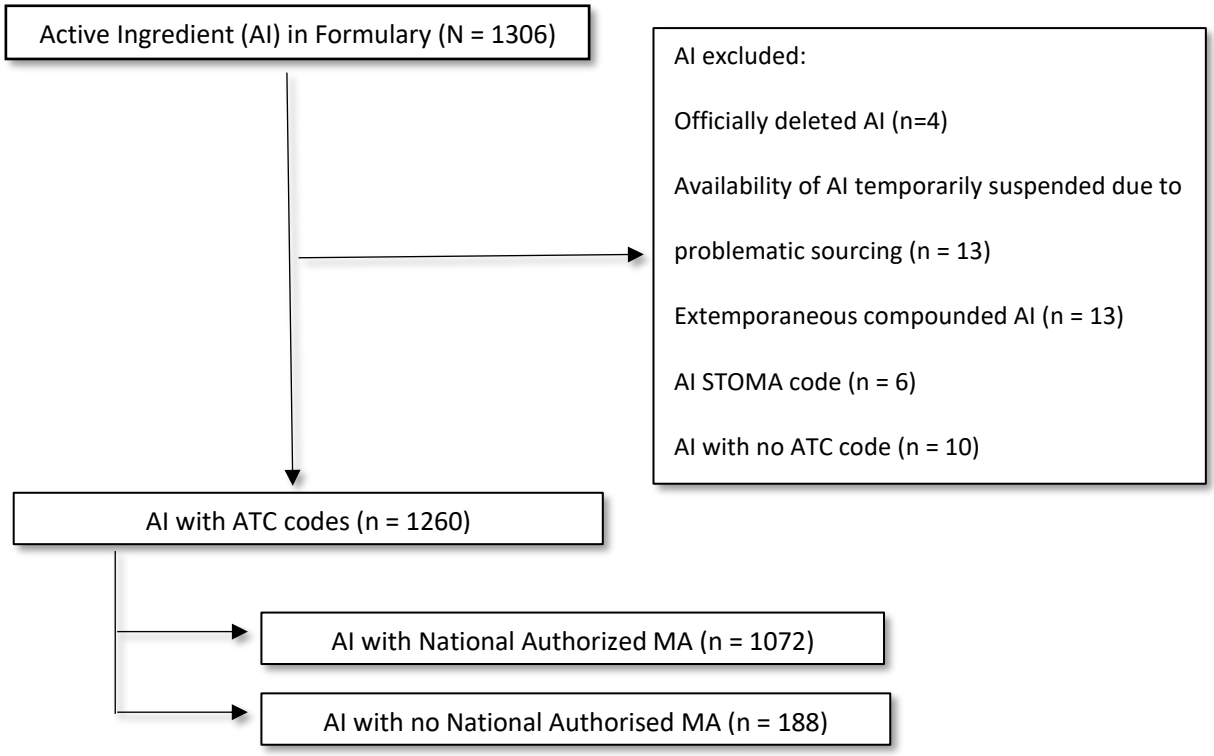

Figure 3.1: Active Ingredients in the Government Formulary List with and without National Authorized Marketing Authorization

The AI with no National Authorized MA were identified and sorted into their Disease Category as stated in the GFL is summarized on Table 3.1.

Table 3.1: Disease Category of Active Ingredients without Marketing Authorization

Disease Category	(N = 188)
Anesthesia	5
Antidotes	6
Cardiovascular System	5
Central Nervous System	9
Contrast Media	3
Ear, Nose and Oropharynx	7
Endocrine System	4
Eye	3
Food Supplements	20
Gastro-intestinal System	5
Immunological Products and Vaccines	13
Infections	23
Malignant Disease and Immunosuppression	25
Miscellaneous	5
Musculoskeletal and Joint Diseases	2
Nutrition and Blood	21
Obstetrics, Gynecology and Urinary Tract Disorders	4
Radiopharmaceuticals	5
Respiratory System	9
Skin	14

From the 188 AI with no National Authorized MA, 11 of them had MA previously held in the UK and for 4 there were no requests for exemption from the requirement of a marketing authorization on the basis of Article 20. (Table 3.2)

Table 3.2: Formulary Items that had their MA held in the UK (N = 11)

Active Ingredient	Dose & Route of Administration	ATC Code	Article 20
Bupivacaine + Adrenaline	2.5mg/mL + 1:200,000 in 10mL Injection	N01BB51	Yes
Bupivacaine + Adrenaline	2.5mg/mL + 1:200,000 in 10mL Injection	N01BB51	Yes
Gadolinium-based Contrast Media	7.5 mL Pre-filled Syringes	V08CA	No
Gadolinium-based Contrast Media	10 mL Pre-filled Syringes	V08CA	No
Acetylcysteine (stand-by)	5% Eye Drops	S01XA08	Yes
Budesonide	2mg/100mL Retention Enema	A07EA	Yes
Co-Danthramer	75/1000 in 5mL Oral Suspension	A06AB53	No
Phenol	5% Oily Injection	C05BB05	Yes
Prednisolone	20mg/100mL Retention Enema	A07EA01	Yes
Rifabutin	150mg Capsules	J04AB04	Yes
Vitamin E (Alpha Tocopheryl)	500mg/5mL Oral Suspension	A11HA03	No

From the 4 medicines that were not granted exemptions on the basis of Article 20, substitutes available in the GFL were identified as shown in Table 3.3.

Table 3.3 Alternatives for medicines in the GFL that were not granted Article 20

Active Ingredient	Dose & Route of Administration	ATC Code	Substitutes available in the GFL
Gadolinium-based Contrast Media	7.5 mL Pre-filled Syringes	V08CA	Gadoxetic Acid Solution for Injection (V08CA10)
Gadolinium-based Contrast Media	10 mL Pre-filled Syringes	V08CA	Gadoxetic Acid Solution for Injection (V08CA10)
Co-Danthramer	75/1000 in 5mL Oral Suspension	A06AB53	Senna tablets (A06AB06) Bisacodyl suppositories / tablets (A06AB02)
Vitamin E (Alpha Tocopheryl)	500mg/5mL Oral Suspension	A11HA03	Vitamin E capsules / tablets (A11HA03)

3.1.2 Review of the Malta Medicines Authority Marketing Authorization Database

A total of 542 MA with the MA Holder based in the UK were withdrawn by the companies and a total of 544 MA were Invalidated MA from the UK because they

no longer met requirements in the EU legislation.

3.1.2.1 Review of Withdrawn MAs from the UK

Withdrawn MAs from the UK were identified (N = 542) and categorized based on their ATC codes as shown in Figure 3.2. Drugs acting on the nervous system (n = 128), antineoplastic agents (n = 64), and drugs acting on the respiratory system (n = 59) are the categories with the most withdrawn MA.

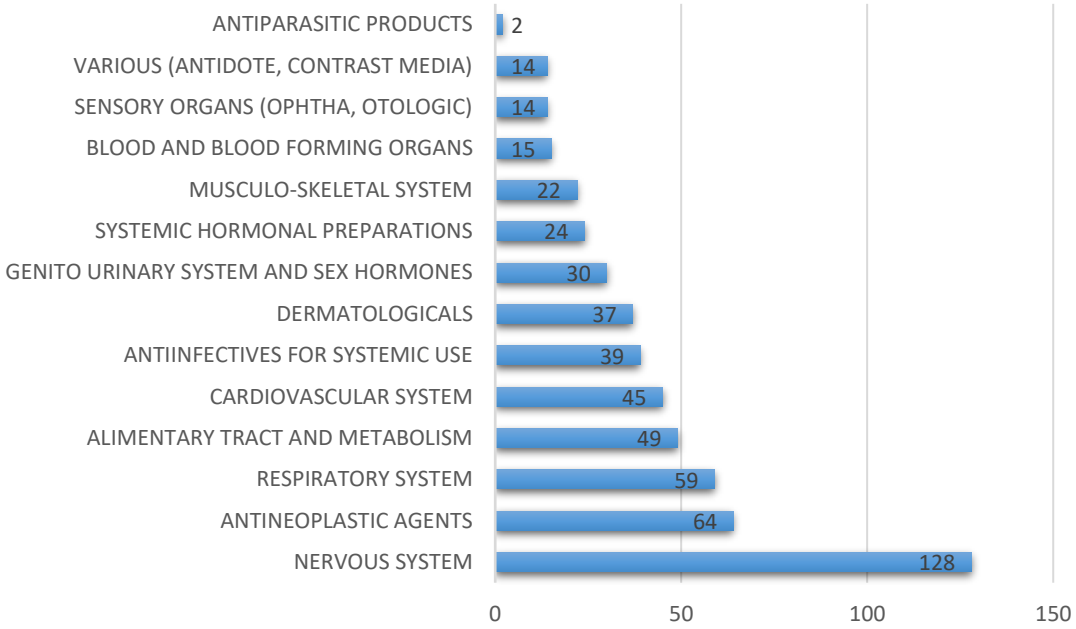

Figure 3.2: Withdrawn Marketing Authorization from UK categorized on ATC Code (N = 542)

Withdrawn MAs were reviewed with current Authorized MA to identify if the same medicine product has an Authorized MA available (Figure 3.3). For the 128 drugs acting on the nervous system with Withdrawn MA, 79 of these have identical Authorized MA available. Fifty-two out of the 64 Antineoplastic agents have identical Authorized MA available. While out of the 59 Withdrawn MA of drugs acting on the respiratory system, only 21 have identical Authorized MA

available.

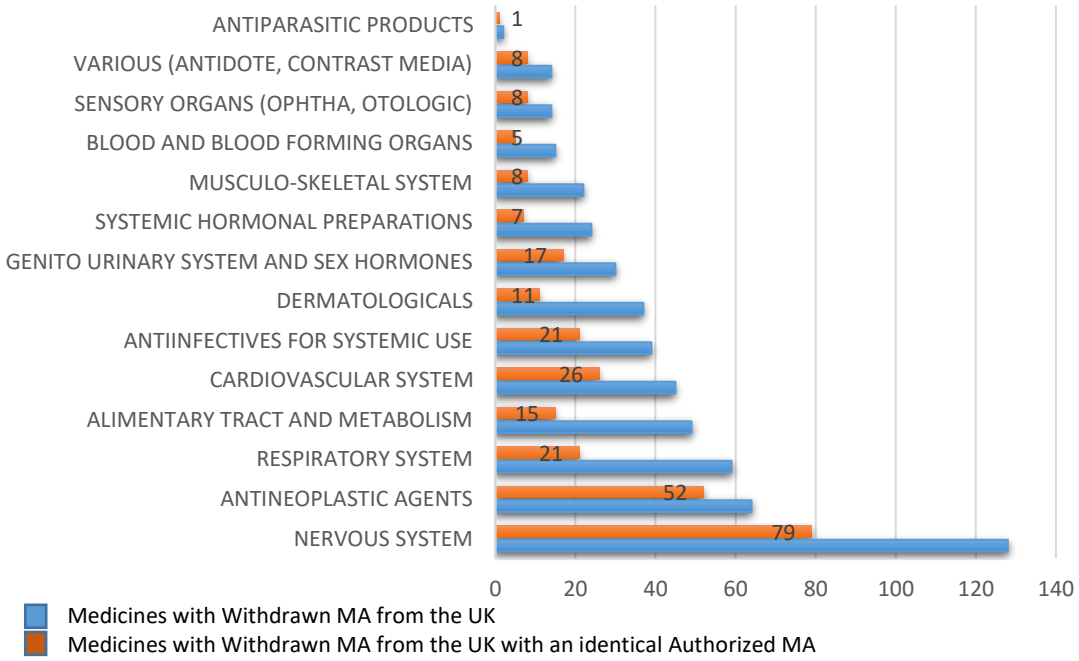

Figure 3.3: Identical Medicine Products with Withdrawn Marketing Authorization from the UK with Authorized Marketing Authorization (N= 277)

Antiparasitic Products – ATC Code P

From the 2 medicines with Withdrawn MA, 1 medicine had an identical reinstated Authorized MA and the other medicine had an alternative Authorized MA.

Various (Antidote, Contrast media) – ATC Code V

From the 14 medicines with Withdrawn MA, 8 medicines had an identical Authorized MA and 5 medicines had an alternative Authorized MA and 1 medicines had no available Authorized MA (Table 3.4).

Table 3.4: Medicines with ATC Code V that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Magnevist	Gadopentate Dimeglumine mg/mL	V08CA01	No	Gadoxetic Acid (V08CA10) Gadobutrol (V08CA09) Gadoteric Acid (V08CA02)

Sensory Organs (Ophthalmological / Otologic) – ATC Code S

From the 14 medicines with Withdrawn MA, 8 medicines had an identical Authorized MA and 4 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.5).

Table 3.5: Medicine with ATC Code S that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Bimatoprost 0.3mg/mL eye drops, solution	Bimatoprost 0.3 mg/mL	S01EE03	No	Latanoprost (S01EE01) Tafluprost (S01EE05)

Blood and Blood forming Organs – ATC Code B

From the 15 medicines with Withdrawn MA, 5 medicines had an identical Authorized MA and 6 medicines had an alternative Authorized MA and 4 medicines had no available Authorized MA (Appendix 3).

Drugs acting on the Musculo-Skeletal System – ATC Code M

From the 22 medicines with Withdrawn MA, 8 medicines had an identical Authorized MA and 9 medicines had an alternative Authorized MA and 5 medicines had no available Authorized MA (Appendix 4).

Systemic Hormonal Preparations – ATC Code H

From the 24 medicines with Withdrawn MA, 7 medicines had an identical Authorized MA and 16 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.6).

Table 3.6: Medicine with ATC Code H that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Pitressin 20 PU/mL Solution for Injection	Argipressin 20 PU/mL	H01BA01	No	Desmopressin(H01BA02) Terlipressin (H01BA04)

Genito-urinary System and Sex Hormones – ATC Code G

From the 30 medicines with Withdrawn MA, 17 medicines had an identical

Authorized MA and 11 medicines had an alternative Authorized MA and 2 medicines had no available Authorized MA (Table 3.7).

Table 3.7: Medicines with ATC Code G that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Pro-viron	Mesterolone 25 mg	G03BB01	No	Testosterone Undecanoate (G03BA03) Testosterone Enanthate (G03BA03)
Canesten Oasis	Sodium Citrate Dihydrate 4 g	G04BX	Yes	

Dermatologicals – ATC Code D

From the 37 medicines with Withdrawn MA, 11 medicines had an identical Authorized MA and 16 medicines had an alternative Authorized MA and 10 medicines had no available Authorized MA (Appendix 5).

Antiinfectives for Systemic Use – ATC Code J

From the 39 medicines with Withdrawn MA, 21 medicines had an identical Authorized MA and 17 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.8).

Table 3.8: Medicine with ATC Code J that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Valtrex Tablet, Film-coated 500 mg	Valaciclovir 500 mg	J05AB11	No	Valganciclovir (J05AB14) Aciclovir (J05AB01)

Drugs acting on the Cardiovascular System – ATC Code C

From the 45 medicines with Withdrawn MA, 26 medicines had an identical Authorized MA and 8 medicines had an alternative Authorized MA and 9 medicines had no available Authorized MA (Appendix 6).

Drugs acting on the Alimentary tract and Metabolism – ATC Code A

From the 49 medicines with Withdrawn MA, 15 medicines had an identical Authorized MA and 26 medicines had an alternative Authorized MA and 8 medicines had no available Authorized MA (Appendix 7).

Drugs acting on the Respiratory System – ATC Code R

From the 59 medicines with Withdrawn MA, 21 medicines had an identical Authorized MA and 29 medicines had an alternative Authorized MA and 9 medicines had no available Authorized MA (Appendix 8).

Antineoplastic Agents – ATC Code L

From the 64 medicines with Withdrawn MA, 52 medicines had an identical Authorized MA and 12 medicines had an alternative Authorized MA.

Drugs acting on the Nervous System – ATC Code N

From the 128 medicines with Withdrawn MA, 79 medicines had an identical Authorized MA and 53 medicines had an alternative Authorized MA and 3 medicines had no available Authorized MA (Appendix 9).

3.1.2.2 Review of Invalidated MAs from the UK

Invalidated MAs from the UK were identified (N = 544) and categorized based on their ATC codes as shown in Figure 3.4. Drugs acting on the nervous system (n = 112), antiinfectives for systemic use (n = 71), and drugs acting on the cardiovascular system (n = 66) are the categories with the most invalidated MA.

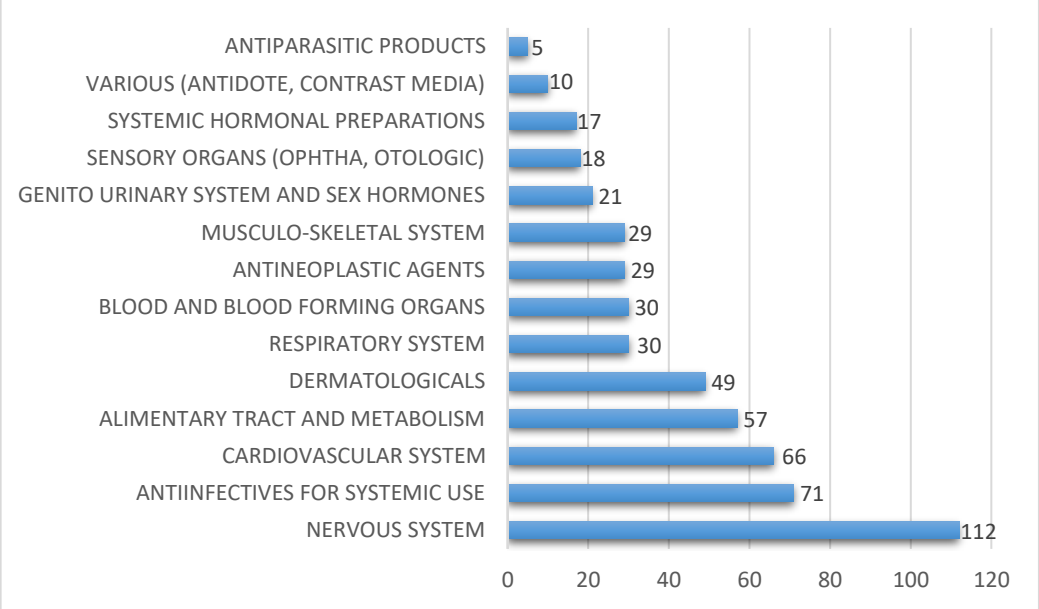

Figure 3.4: Invalidated Marketing Authorization from UK categorized on ATC Code (N = 544)

Invalidated MAs were reviewed with current Authorized MA to identify if the same medicine product has an Authorized MA available (Figure 3.5). For the 112 drugs acting on the nervous system with Invalidated MA, 108 of these have identical Authorized MA available. Sixty-nine out of the 71 antiinfectives for systemic use have identical Authorized MA available. While out of the 66 Invalidated MA of drugs acting on the cardiovascular system, 62 have identical

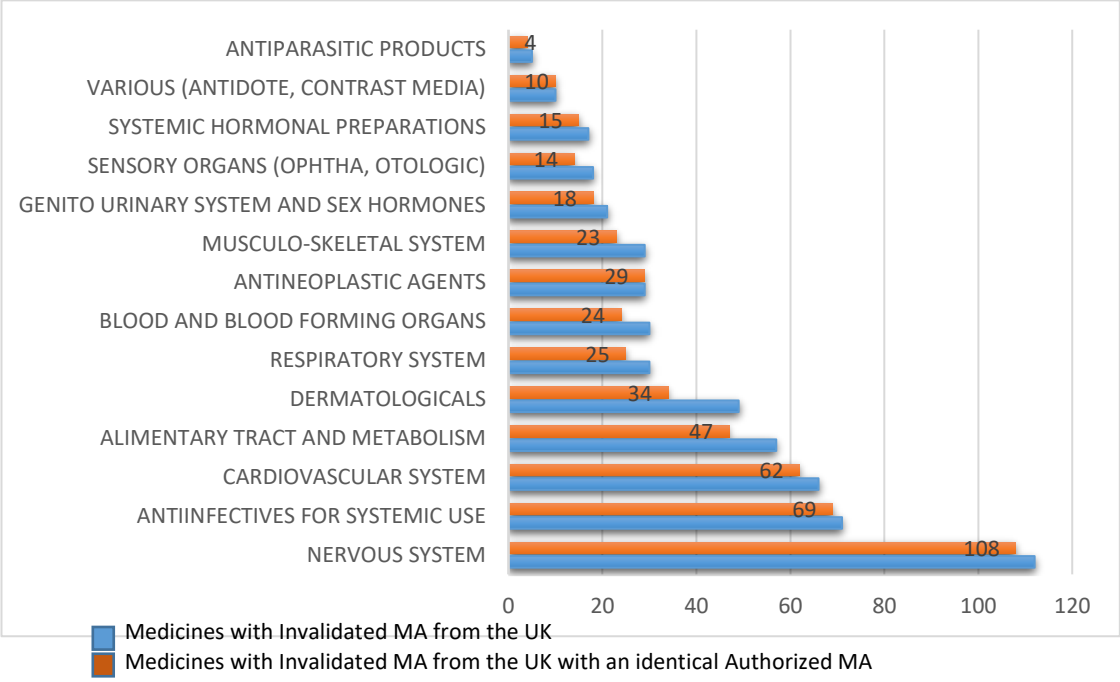

Figure 3.5: Identical Medicine Products with Invalidated Marketing Authorization from the UK with Authorized Marketing Authorization (N= 481)

Antiparasitic Products – ATC Code P

From the 5 medicines with Invalidated MA, 4 medicines had an identical Authorized MA and 1 medicine had no available Authorized MA (Table 3.9).

Table 3.9: Medicine with ATC Code P that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Eurax Cream 10%	Crotamiton 10 %	P03AX	Yes	

Various (Antidote, Contrast media) – ATC Code V

From the 10 medicines with Invalidated MA, 10 medicines had an identical Authorized MA.

Systemic Hormonal Preparations – ATC Code H

From the 17 medicines with Invalidated MA, 15 medicines had an identical Authorized MA and 1 medicine had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.10).

Table 3.10: Medicines with ATC Code H that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Argipressin Solution for Injection 20 IU/ml	Argipressin 20 IU/mL	H01BA01	No	Desmopressin(H01BA02) Terlipressin (H01BA04)

Sensory Organs (Ophthalmological / Otologic) – ATC Code S

From the 18 medicines with Invalidated MA, 14 medicines had an identical Authorized MA and 1 medicine had an alternative Authorized MA and 3 medicines had no available Authorized MA (Table 3.11).

Table 3.11: Medicines with ATC Code S that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Golden Eye Eye Ointment 0.15% w/w	Dibrompropamidine Isetionate 0.15% w/w	S01AX14	No	Bibrocathol (S01AX05)
Golden Eye Eye Drops Solution 0.1% w/v	Propamidine Isetionate 0.1% w/v	S01AX15	No	Bibrocathol (S01AX05)
Sofradex Ear/Eye Drops, Solution	Framycetin Sulfate 5 mg/mL | Gramicidin 0.05 mg/mL | Dexamethasone 0.05 mg/mL	S03CA01	No	Gentamicin Sulfate (S03AA06)

Genito-urinary System and Sex Hormones – ATC Code G

From the 21 medicines with Invalidated MA, 18 medicines had an identical Authorized MA and 1 medicine had an alternative Authorized MA and 2 medicines had no available Authorized MA (Table 3.12).

Table 3.12: Medicines with ATC Code G that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Hytrin Tablets 2mg	Terazosin 2 mg	G04CA03	No	Alfuzosin Hydrochloride (G04CA01) Tamsulosin Hydrochloride (G04CA02)
Hytrin Tablets 5mg	Terazosin 5 mg	G04CA03	No	Alfuzosin Hydrochloride (G04CA01) Tamsulosin Hydrochloride (G04CA02)

Drugs acting on the Musculo-Skeletal System – ATC Code M

From the 29 medicines with Invalidated MA, 23 medicines had an identical Authorized MA and 5 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.13).

Table 3.13: Medicines with ATC Code M that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Radian B Pain Relief Spray	Camphor 0.6 % w/v | Acetylsalicylic Acid 1.2% w/v | Methyl Salicylate 0.6% w/v | Menthol 1.4% w/v	M02AC	No	Diethylamine Salicylate | Heparin Sodium | Menthol (M02AC) Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)

Antineoplastic Agents – ATC Code L

From the 29 medicines with Invalidated MA, 29 medicines had an identical Authorized MA.

Blood and Blood forming Organs – ATC Code B

From the 30 medicines with Invalidated MA, 24 medicines had an identical Authorized MA and 4 medicines had an alternative Authorized MA and 2 medicines had no available Authorized MA (Table 3.14).

Table 3.14: Medicines with ATC Code B that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Sodium Citrate 0.3M Oral Solution	Sodium Citrate 2.647/30 g/mL	B05CB02	Yes	
Sando-K 0.6 g/0.4 g Effervescent Tablets	Potassium Chloride 0.6 g | Potassium Bicarbonate 0.4 g	B05XA01	Yes	

Drugs acting on the Respiratory System – ATC Code R

From the 30 medicines with Invalidated MA, 25 medicines had an identical Authorized MA and 3 medicine had an alternative Authorized MA and 2 medicine had no available Authorized MA (Table 3.15).

Table 3.15: Medicines with ATC Code R that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Covonia Dry Cough Sugar Free Formula Oral Solution 5mg/5ml	Pholcodine 5 mg/mL	R05D	No	Dextromethorphan Hydrobromide (R05DA09) Butamirate Citrate (R05DB13) Levodropropizine (R05DB27) Codeine Phosphate (R05DA04)
Galcodine Linctus Care Codeine Sugar Free Oral Solution 15mg/5ml	Codeine Phosphate 15 mg/5 mL	R05DA04	Yes	

Dermatologicals – ATC Code D

From the 49 medicines with Invalidated MA, 34 medicines had an identical Authorized MA and 11 medicines had an alternative Authorized MA and 4 medicine had no available Authorized MA (Appendix 10).

Drugs acting on the Alimentary tract and Metabolism – ATC Code A

From the 57 medicines with Invalidated MA, 47 medicines had an identical Authorized MA and 9 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.16).

Table 3.16: Medicine with ATC Code A that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Clove Oil Dental Solution 100% v/v	Clove Oil 100 % v/v	A01AD	No	Benzydamine Hydrochloride (A01AD02)

Drugs acting on the Cardiovascular System – ATC Code C

From the 66 medicines with Invalidated MA, 62 medicines had an identical Authorized MA and 3 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.17).

Table 3.17: Medicine with ATC Code C that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Oily Phenol Injection Solution for Injection 5% w/v	Phenol	C05BB05	Yes	

Antiinfectives for Systemic Use – ATC Code J

From the 71 medicines with Invalidated MA, 69 medicines had an identical Authorized MA and 2 medicines had an alternative Authorized MA.

Drugs acting on the Nervous System – ATC Code N

From the 112 medicines with Invalidated MA, 108 medicines had an identical Authorized MA and 3 medicines had an alternative Authorized MA and 1 medicine had no available Authorized MA (Table 3.18).

Table 3.18: Medicine with ATC Code N that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Bupivacaine and Adrenaline (Epinephrine) Injection 0.25% w/v, 1 in 200,000	Bupivacaine Hydrochloride 25 mg | Adrenaline 0.05 mg	N01BB51	Yes	

3.2 Phase 2 – Semi-structured Interview

Individual semi-structured interviews were carried out to determine the stakeholder's views and experiences post-Brexit. Questions involved facilitated discussion on what challenges they have encountered and how the over-all experience has defined the current state of medicine availability in Malta. Twenty-nine stakeholders participated which included 15 pharmacists practicing in community pharmacies, 6 pharmacist practicing at the hospital, 3 from regulatory, and 5 wholesalers.

The main themes of the challenges reported by the stakeholders (N = 29) included: "*Financial costs*" (n = 26); "*Brexit is an unprecedented event*" (n = 23); and "*Public's attitude with medicines*" (n = 21). Appendix 11 provides a summary of recurring ideas and themes.

Theme 1: Financial costs

Direct and indirect expenses were mentioned by the stakeholders. Wholesalers stated the burden of application and reapplication fees, shipping and logistic costs, and repackaging or labelling requirement costs that they have borne.

"The fees for the applications and reapplications is an additional cost."

"We did not have to spend on repackaging and relabeling since the medicines are in English."

"Sourcing from the UK was cheaper in the sense that there were established shipping deals compared to having to negotiate new ones from new suppliers in other EU countries."

This would entail a price increase in the medicines that the patient's would have to shoulder, a concern shared by community pharmacists (n = 13) and hospital pharmacists (n = 4). Community pharmacists also stated that alternatives available in their pharmacies have been noted to have increased in price.

"Some of the alternatives available are have a higher price. It may not be much but it adds up."

"Medicines not available can delay patient treatment and prolong their hospital stay."

"When treatment has to be shifted it could have additional cost to the patient."

Theme 2: Brexit is an unprecedented event

Brexit is a unique event set in particular circumstances that has never occurred before and there is no definitive course of action moving forward that stakeholders can follow to come out on the other side with minimal consequences.

"As far as I know, Brexit is a quite a bit of an exceptional situation. The way the EU was set-up is unique."

"This is like a first time for everyone. It feels like an experiment that can really affect a lot of people in real time."

"This is a new thing, and the market is reacting to what is happening. We have no guide moving forward."

Everyone involved is taking each circumstance as it arises with agency leaders in the industry doing their best to forecast and plan but there is only so much one can prepare for.

"Authorities were doing their best but obviously this is not something that happens often."

"With Brexit, stakeholders can plan well but cannot perfectly see how the events would unfold."

"The protocols moving forward are untested. It's more we see how this goes and adjust."

Theme 3: Public's attitude with medicines

Generations have grown up used to certain medicines and the bias of

consumers to the medicines they are accustomed to, is not something easily swayed.

> "*Some patient's would rather not buy when they cannot find the brand they prefer."*
>
> *"Patients have gotten used to a certain brand that it is a household name and do not think that other medicines that are similar work as effectively."*

Suppliers trying to introduce alternative medicines market as substitutes to those no longer available may not be economically viable as the consumers would have their hesitations.

> "*Sometimes marketing a product is not viable as the public would not respond well to it."*
>
> "*When we introduce an alternative in the market there is additional effort to market it, to make the public aware and to get them to trust the product. It takes time. It is not something instant."*

The interviewees unanimously stated (n = 29) that the unavailable medicines are caused by several events happening concurrently such as the Covid-19 pandemic, escalating conflicts between nations, reports of API manufacturing concerns; but Brexit had a significant impact on medicine availability with Malta's supply.

> *"This is a complex issue. It's difficult to separate which medicines are not available because of Brexit or because of several other things."*

"We try our best but there are many factors to consider, not just Brexit, we experienced a pandemic and the war."

"It was a perfect storm with world-wide shortages and Covid and then add on Brexit. We had to go through it almost all at the time."

"Perception may be that Brexit is the easiest to blame for unavailable medicines but that would be untrue and unfair."

To help facilitate the discussion, questions answerable by a Likert scale was asked to the stakeholders.

The first question was on the ease of medicines in Malta post-Brexit. A majority (n = 25) of the stakeholders found it slightly harder for medicines to be available in Malta post-Brexit. Three of the stakeholders stated that it was harder and 1 felt that there was no difference.

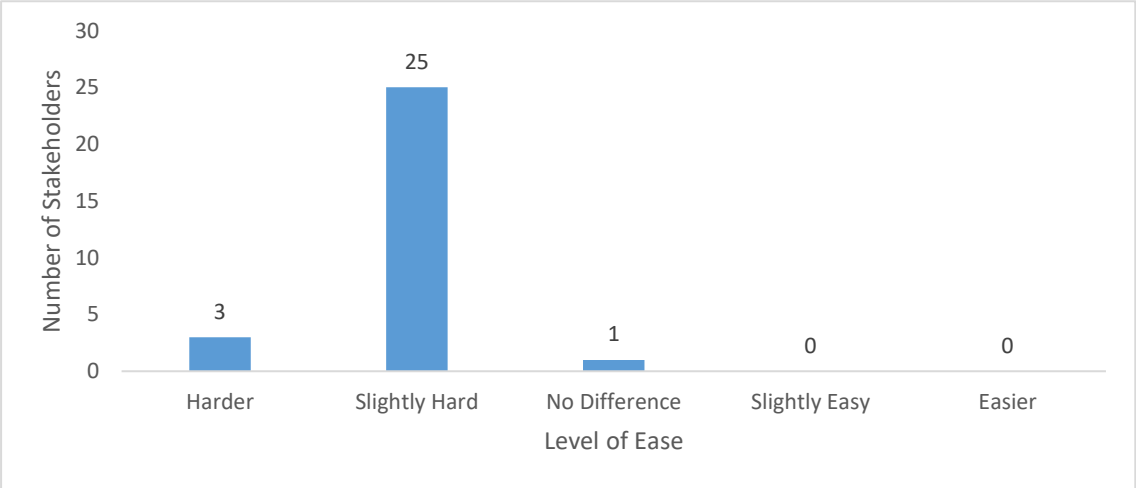

Figure 3.6: Ease of medicine availability in Malta post-Brexit (N = 29)

The stakeholders were asked the difference on medicine availability pre- and post-Brexit. Most (n = 23) of the stakeholders felt a moderate difference in medicine availability pre- and post-Brexit in their field of practice in Malta. Two were more inclined to think that there was a severe difference, the other 2 found the difference between medicine availability pre- and post-Brexit to be a major difference and 2 other stakeholders found only a minor difference in their experience.

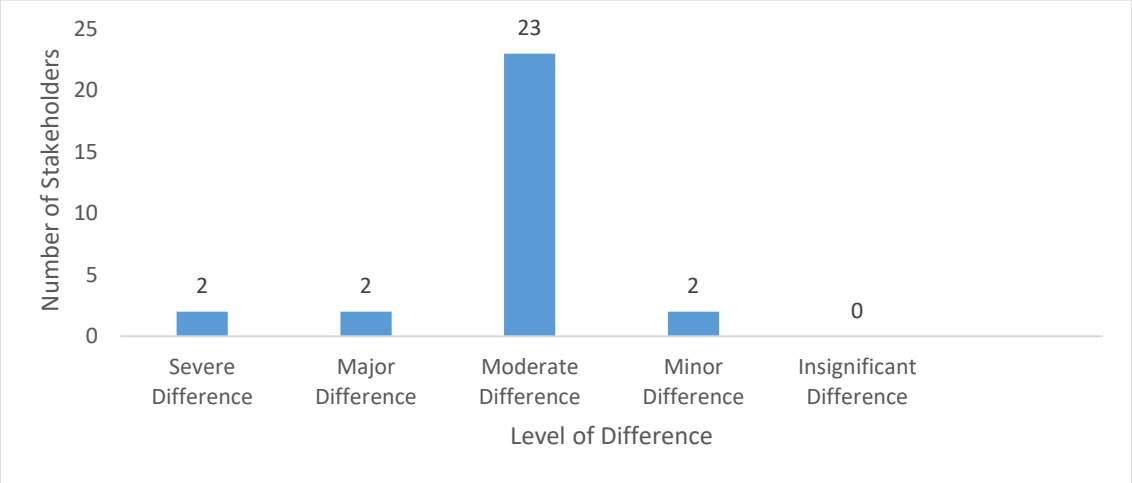

Figure 3.7: Difference on medicine availability pre- and post-Brexit (N = 29)

The effect of medicine availability post-Brexit to patient treatment was asked. Twenty-four of the interviewees found that in their field of practice there is a moderate effect of medicine availability post-Brexit to patient treatment. Three of them think there was a major effect and 2 felt that it had a minor effect.

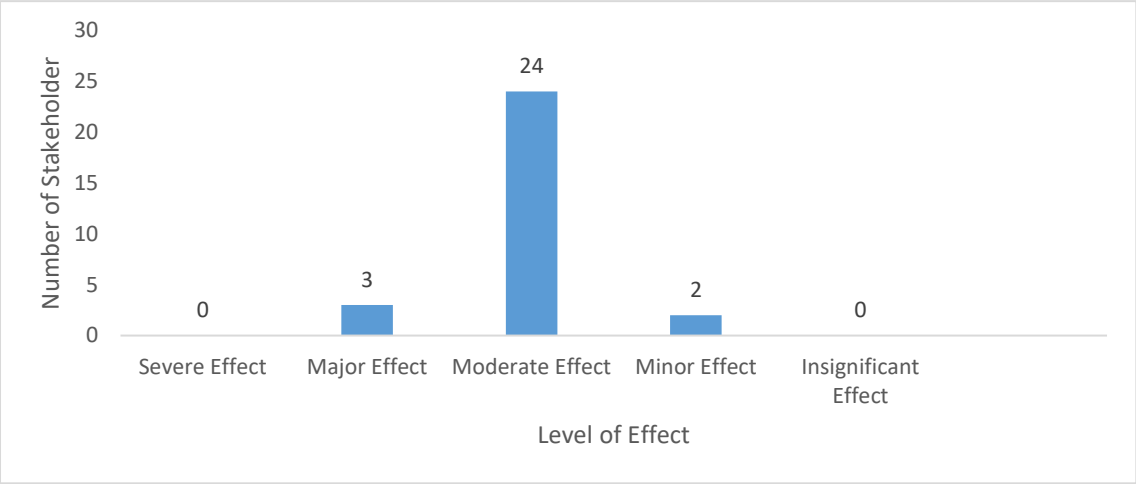

Figure 3.8: Effect of medicine availability post-Brexit to patient treatment (N = 29)

The last question was how ready Malta was for Brexit. A few (n = 3) and some (n = 7) felt that Malta was only slightly ready and somewhat ready, respectively; most of the stakeholders (n = 19) felt that Malta was very ready when it came to Brexit.

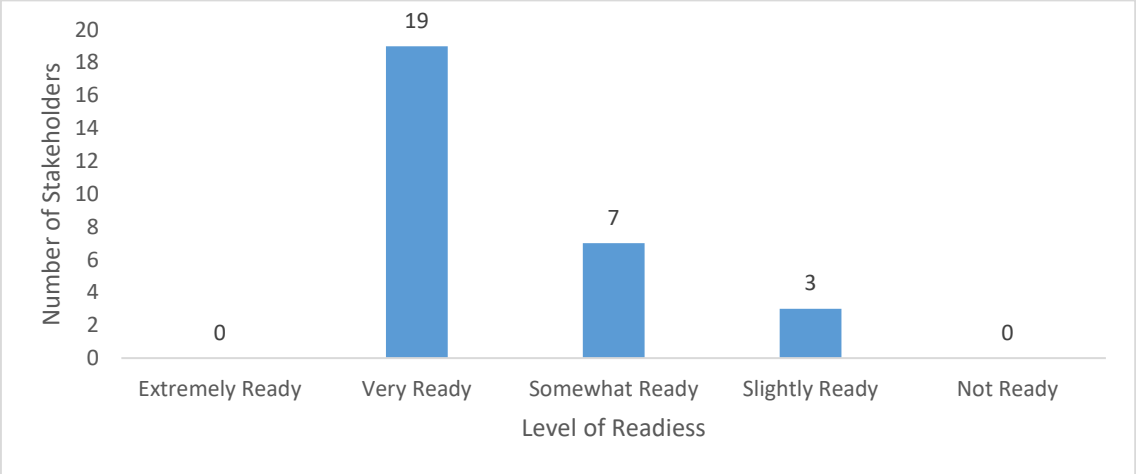

Figure 3.9: Malta's readiness for Brexit (N = 29)

The stakeholders expressed recommendations that would improve medicine availability in a post-Brexit landscape.

One recommendation is an increase communication among stakeholders. Stakeholders have noticed a disconnect between the different sectors and are hopeful that a more clear path of communication moving forward would be established for the benefit of everyone involved.

> *"I am uncertain to whether certain products are permanently unavailable or it is just a temporary issue."*
>
> *"There are no clear statements from involved parties. At least from my end, I have heard no reassurance from the government about the issue."*
>
> *"If maybe, we could get an advance notice from suppliers when there are supply problems, we can prepare our patients and act accordingly."*
>
> *"When patients ask me when a medicine is coming back, I don't feel good when I tell them that we don't know."*

Easily accessible centralized information system was also suggested. The interviewees grant that there is information available but they also expressed some difficulty in receiving timely updates and finding all the relevant information they needed.

> *"Sometimes, there are medicines that are unavailable but my patients are telling me that they heard that it is available already."*
>
> *"I try to stay updated but it gets hard when I go online and I'm not sure which sources to trust that are updated."*

"I know the authorities are doing their best but if I don't actively look up the information, I won't know what is happening."

It was recommended that more effort be placed on continued education that involves healthcare workers and public information dissemination and generic awareness. Healthcare workers being well-informed in what medicines are out of stock and what alternatives are available in Malta would help in maintaining control of any out of stock situations. Community pharmacists are the first line when it comes to managing the most common medicines needed by the public.

"In the case of some health care workers, they are unaware of which medicines are currently not present in Malta."

"It's more work, of course, to know what is available at the moment and what other alternatives there are, but we have to do more to serve our patients."

It was proposed that more emphasis should be placed on spreading correct and timely information to the public. A more public information dissemination would give a semblance of control to the general population and allow a sense of involvement. Generic awareness makes consumers more comfortable in switching to a different brand of their medication rather than sacrificing treatment.

"I have clients who refuse to try a different brand because that is not what the doctor prescribe. It's a bit hard to try to convince them."

"Patients would rather try to go to other pharmacies to look for the brand

they want even if I already told them it is out of stock at the moment."

"It makes me feel helpless when patients don't get the medicine they want and we do not have anything else to offer.

Chapter Four

Discussion

4.1 Post-Brexit and Availability of Medicines

Medicine unavailability has impacts on economic, clinical, and humanistic levels (Phuong et al., 2019). Shukar et al., (2021) stated that for the stakeholders involved, especially patients, unavailable medicines often result in higher costs across all economic areas. This has been found by this study to be relevant to Malta. Stakeholders must take additional steps to manage the shortage. Pharmacists practicing in the hospital and community have no choice but to start compounding, make logistical changes, buy medications in short supply at higher prices, or acquire pricey alternative brands. Patients' out-of-pocket expenses grow as a result of having to pay more for expensive brands, costly substitutes, and other indirect medication fees. Patients spend more for longer therapy, prolonged hospital stays, and inferior treatment (Alruthia et al., 2018).

Early in 2023, Malta found itself in a situation with unavailable antibiotic syrups. The unavailability of one of the most prescribed antibiotic syrup led to an increase in the demand for other alternative syrups which pharmacies were unprepared for. Antimicrobial medicine shortages are serious because they can result in delayed treatment and persistent infections (Ventola, 2015). Another scenario described during the stakeholders' interviews was when over-the-counter flu medications Beechams® and Lemsip®, were no longer available; community pharmacists mentioned that they still got patients asking for it who refused to try other over-the-counter flu medications citing their preference for the powder dosage form that needs to be diluted in water over flu medications in tablet form. It is interesting to take into account how patient's respond to what alternatives are currently available in the market as this affects demand.

Medication unavailability had a variety of humanistic effects on patients, healthcare workers, and other stakeholders. Physicians must choose which patients will receive the few drugs that are available, or they must choose an alternative form of treatment that may not be as effective as the original medicine of choice. The limitation in available options, limits the prescribers treatment options. Healthcare workers are more likely to experience workplace frustration. The research found pharmacists being disheartened when they have to tell their patients that the medicines they want are not available and cannot provide a specific answer when asked when the medication would be available. The management of the shortages requires more time and effort (Walker et al., 2017; Phuong et al., 2019).

The identified medicines with withdrawn or invalidated MA from the UK that had no Authorized MA were not consequential since therapeutic substitutes were available. For example Inegy® which has Ezetimide + Simvastatin as the active ingredient had Lipocomb® which has Ezetimide + Rosuvastatin as its therapeutic substitute. Another example is, Valacyclovir tablets had Acyclovir tablets as its therapeutic substitute. Medicines with Withdrawn MA that were considered as life-saving medicines such as those in the Antineoplastic category all had Authorized MA. The derogations and use of Article 20 provided regulatory flexibility in ensuring that essential medicines are available. The European Federation of Pharmaceutical Industries and Associations has resolved that regulatory flexibility helps prevent and mitigate shortages and a case-by-case approach is needed in circumstances that could jeopardize the patients' supply of

medications.[42]

Medicines in the GFL are considered essential medicines, only 4 medicines in the GFL had withdrawn MA from the UK and all 4 had therapeutic substitutes that are found in the GFL as well. It is of interest to note that from the 188 medicines in the GFL with withdrawn MA, only 11 were from the UK. It infers the idea that more than Brexit has affected medicine unavailability in Malta. Brexit may be the visible convenient reason to blame on medicine unavailability, but it is certainly not the only cause. The interviewees unanimously stated that the unavailable medicines are caused by several events happening concurrently such as the Covid-19 pandemic, escalating conflicts between nations, reports of API manufacturing concerns. The Covid-19 pandemic affected the on-going negotiations and collaborations between the UK and the EU, even creating tension when it came to vaccine availability (Fernando et al., 2020; Glencross, 2021). To stop the spread of Covid-19, the majority of EU countries have placed border restrictions. These restrictions disrupted supply chains, including medicines and medical supplies (Mircheva, 2020.) Disentangling the effects of a global pandemic from the effects of Brexit prove to be difficult (Hantrais, 2021). To exclusively place the burden of fault of medicine unavailability on Brexit would be misleading and discounts the other global events and its direct and indirect effect on medicine availability.

Aside from Brexit, there are other circumstances that result in medicine unavailability.

[42] European Federation of Pharmaceutical Industries and Associations. Addressing the Root Causes of Medicines Shortages: Supply Chain Stakeholders' Views on Root causes and Solutions. [Internet]. 2019 [cited 04 June 2023]. Available from: https://www.efpia.eu/media/413378/addressing-the-root-causes-of-medicines-shortages-final-051219.pdf

Manufacturing problems due to issues with the production line, quality control issues, or supply chain disruptions.[43] Since the UK has been a key player in the EMA, which regulates medicines across the EU, delays in the approval of new medicines and regulatory hurdles for medicines that are already approved could impact the availability of medicines in countries that rely on the EMA for their approval processes.[44] Stockpiling of certain medicines can also cause medicine unavailability. This occurs when there is a sudden increase in demand for a particular medication, leading to a shortage of supply.[45] Brexit impacted intellectual property laws, which could limit the availability of affordable generic medicines in other countries. This could lead to higher prices and reduced availability of certain medicines [46] (Tenni et al., 2022).

For patients to access these medicines several other dimensions are in play: acceptability, accessibility, accommodation, affordability, availability and awareness (Penchansky and Thomas (1981); Saurman (2016)). Ensuring that medicines have Authorized MA is a primary regulatory measure that permits availability of medicine in the country. Medicines are made available through the MA, however, patients may not have timely access to them due to other elements such as production problems, delivery

[43]Pharma News Intelligence. Finding solutions for drug shortages: Short and long-term management [Internet]. [cited 02 June 2023]. Available from: https://pharmanewsintel.com/features/finding-solutions-for-drug-shortages-short-and-long-term-management

[44] European Medicines Agency. Brexit-related Guidance for Companies [Internet]. 2021 [cited 02 June 2023]. Available from: https://www.ema.europa.eu/en/about-us/brexit-uk-withdrawal-eu/brexit-related-guidance-companies

[45]European Parliament. Addressing Shortages of Medicines. [Internet]. [cited 02 June 2023]. Available from:
https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/649402/EPRS_BRI(2020)649402_EN.pdf

[46] The United Kingdom Parliament. The impact of Brexit on the pharmaceutical sector: Trade opportunities post-Brexit. [Internet]. [cited 02 June 2023]. Available from:
https://publications.parliament.uk/pa/cm201719/cmselect/cmbeis/382/38209.htm

delays and bureaucratic complications. Pharmaceutical companies may file for a medicine's MA but eventually decide that it would not be in their interest to market the medicine in Malta.

The study acknowledges the experiences reported by the stakeholders throughout the circumstances. Brexit has economical costs that affects the UK and the other EU member countries (Sampson, 2017). On a smaller perspective, the financial aspect is felt by the wholesalers, as mentioned in the stakeholders' interview, with the direct expenses such as logistical costs and indirect expenses such as marketing for a new medicine; which consequently affects the selling price of these medicines to the patients. Lorgelly (2018) concluded that with Brexit, health care cost could increase. Brexit is surrounded by uncertainty (Bloom et al., 2018; Graziano et al., 2020), with the novelty and complexity of the situation, it is inevitable that concerns about the unpredictability of the effects in the pharmaceutical supply chain would be shared by the stakeholders. Patient's preference to certain medicines is shaped by their experience. Diederich (2015) found that the general public appears to prioritize therapeutic value, expenses, and evidence based medicine when it comes to the medicine of their choice.

It is important for healthcare systems and governments to address the root causes of these shortages and find solutions to ensure that patients have access to the medications they need. This may involve improving supply chain management, increasing manufacturing capacity, or addressing regulatory issues (Ventola, 2015; Yang et al., 2016).

The UK has steadily supplied medicinal products to small member states such as Cyprus, Ireland, Northern Ireland and Malta in the past. It is the goal of the EC to promote public health through a consistent supply of medicines, and exemptions for certain medications have been published to lessen the impact of Brexit on the market of small member states. Derogations from certain obligations concerning certain medicines are made available to ensure a continued supply of medicines to the smaller Member States.[47] The derogations are temporary as it is expected that in the next few years Malta's medicine market is gradually supplied through other EU Member States.[48] A portion of medicines in Malta had MAs in the UK. Despite the plans put forth in the pharmaceutical sector, there are still factors that can impact the access of medicines between the UK and the EU (Thomas, 2019). From a certain perspective, the derogations are prolonging the process of acquiring a different source of medicines. However, the short-term benefits of the derogations permits allowances in the supply and acts as a buffer while stakeholders source out a more permanent supplier. MAs from the UK that were provided exceptions via the use of Article 20 help cater to the medicine demands of the Maltese population.

[47] Health Products Regulatory Authority. Brexit - Latest Information [Internet]. [cited 02 June 2022]. Available from: http://www.hpra.ie/homepage/about-us/stakeholders/brexit/brexit---latest-information

[48] European Sources Online. Regulation (EU) 2022/641 amending Regulation (EU) No 536/2014 as regards a derogation from certain obligations concerning investigational medicinal products made available in the United Kingdom in respect of Northern Ireland and in Cyprus, Ireland and Malta– European Sources Online [Internet]. 2022 [cited 02 June 2022]. Available from: https://www.europeansources.info/record/proposal-for-a-regulation-amending-regulation-eu-no-536-2014-as-regards-a-derogation-from-certain-obligations-concerning-investigational-medicinal-products-made-available-in-the-united-kingdom-with/

4.2 Limitations of the Research

The study was focused primarily on MA from the UK. Marketing Authorizations from the other countries were not included. Another limitation of the research was that the interviewees were purposively selected based on their field of practice and availability; while this provided an adequate picture, findings cannot be generalized to all stakeholders The topic was also limited to medicine availability with no specific drug classification focus.

4.3 Recommendations

Including MA from other countries is suggested for further research. Increasing the number of participants of the interview would provide a fuller discussion. Inviting clinicians and prescribers offers another perspective. It is recommended to include participants not practicing in the pharmaceutical industry as their point of views when it comes to medicine availability would add more nuance to the research. Targeting patients as the primary participants to gather their opinions and experiences would also be recommended.

It would be of interest to expand the topic on not just the availability of medicines but as well as medical devices or veterinary medicines. Focusing on a specific drug classification, for example the availability of Oral Antibiotics, would also be interesting for further research.

4.4 Conclusion

For member states with small pharmaceutical markets such as Malta, unavailability of medicines is a priority problem. Moving to a post-Brexit setup, sourcing out

pharmaceutical supplies from different EU countries would allow a more stable condition of availability of medicines. Challenges reported by the stakeholders are to be expected considering the novelty of Brexit. Stakeholders' experiences identified areas for improvement and an opportunity to optimize processes. Reviewing the MAs of essential medicines and MAs from the UK provided a scenario where Malta employs the use of measures, primarily regulatory measures, such as the use of Article 20 of the Medicines Act, that exempts from the requirement of having a marketing authorizations in certain circumstances; to address the availability problem. Measures that not only provide short-term solutions and act as a buffer to prevent medicines shortages, but also lay down the ground work in the long run.

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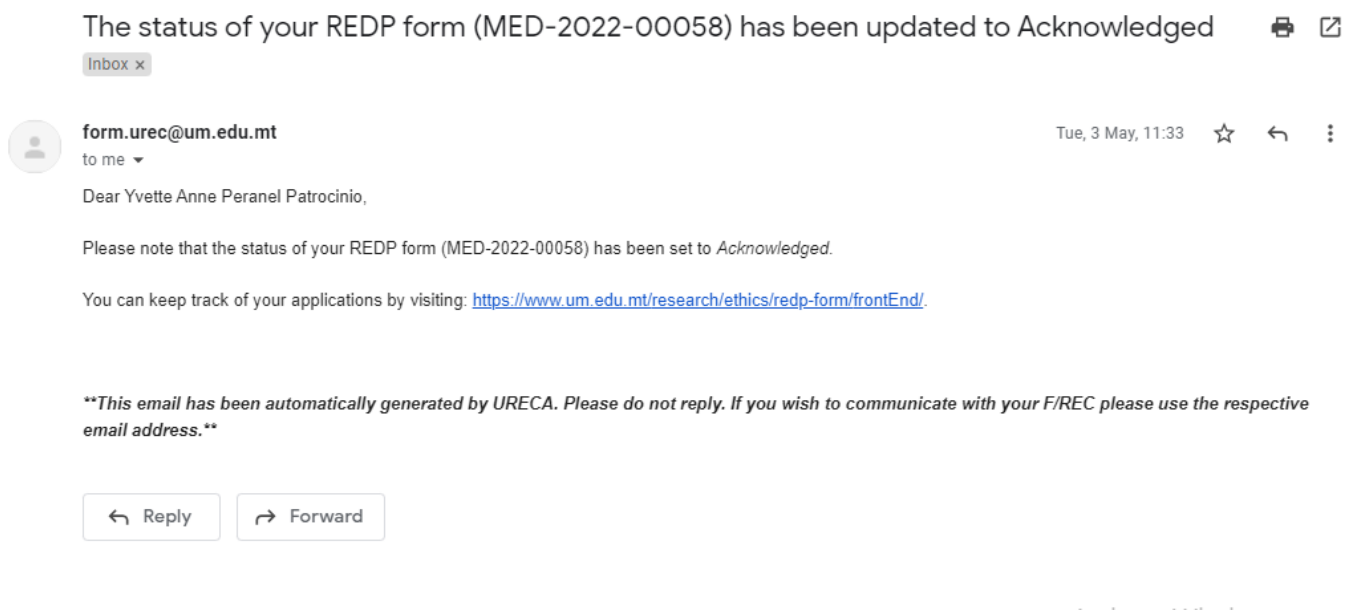
Appendix

Appendix 1: Acknowledgement of the Faculty Research Ethics Committee (FREC) of the University of Malta Faculty of Medicine & Surgery.



The status of your REDP form (MED-2022-00058) has been updated to Acknowledged

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to me

Dear Yvette Anne Peranel Patrocinio,

Please note that the status of your REDP form (MED-2022-00058) has been set to *Acknowledged*.

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Appendix 2: Interview questions answerable by Likert Scale

Has it been harder for medicines to be available in the island after Brexit? On a scale of 1 to 5, with 1 being easier and 5 being harder, how would you rate the availability of medicines post-Brexit?

5	4	3	2	1
Harder	Slightly Hard	No Difference	Slightly Easy	Easier

Based on your current working practice, was the availability of medicines heavily impacted after Brexit? On a scale of 1 to 5, with 1 being No Significant Impact and 5 being Severly Impacted, how would you rate the impact of Brexit on medicine availability?

5	4	3	2	1
Severe Impact	Major Impact	Moderate Impact	Minor Impact	Insignificant Impact

Has patient treatment been affected due to availability of medicines? On a scale of 1 to 5, with 1 being No Significant Effect and 5 being Severe Effect, how would you rate the effect of medicine availability post-Brexit to patient treatment?

5	4	3	2	1
Severe Effect	Major Effect	Moderate Effect	Minor Effect	Insignificant Effect

On a scale of 1 to 5, with 1 being Not ready and 5 being Extremely Ready, how would you rate how would you describe the readiness of Malta's market for Brexit?

5	4	3	2	1
Extremely Ready	Very Ready	Somewhat Ready	Slightly Ready	Not Ready

Appendix 3: Medicines with ATC Code B that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Dindevan 50mg Tablets	Phenindione 50 mg	B01AA02	No	Warfarin (B01AA03)
Dindevan 10mg Tablets	Phenindione 10 mg	B01AA02	No	Warfarin (B01AA03)
Ironorm Capsules	Folic Acid 1.7 mg | Ascorbic Acid 15 mg | Ferrous Sulfate Exsiccated 195 mg | Nicotinamide 10 mg | Thiamine Hydrochloride 1 mg | Riboflavin 2 mg	B03AE02	No	Copper | Iron | Manganese (B03AE10)
Additrace Concentrate for solution for infusion	Chromic Chloride 5.33 mcg| Potassium Iodide 16.6 mcg | Copper Chloride 340 mcg | Ferric Chloride 544 mcg | Zinc Chloride 1.36 mg|	B05XA	No	Chromic Chloride |Copper Chloride | Ferric Chloride | Manganese | Potassium Iodide | Sodium Fluoride | Sodium Molybdate Dihydrate | Sodium

	Manganese Chloride 99 mcg | Sodium Fluoride 210 mcg| Sodium Molybdate 4.85 mcg| Sodium Selenite 10.5 mcg			Selenite | Zinc Chloride (B05XA31) Potassium Iodide | Copper Chloride | Zinc Chloride| Manganese Chloride| Sodium Fluoride | Sodium Selenite (B05XA31)

Appendix 4: Medicines with ATC Code M that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Radian B Muscle Rub	Camphor Oil 0.32 % w/w | Menthol 2.54 % w/w | Methyl Salicylate 0.42 % w/w | Oleoresin Capsicum 0.005 % w/w | Camphor 1.41 % w/w	M02AC	No	Diethylamine Salicylate | Heparin Sodium | Menthol (M02AC) Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)
Radian B Muscle Lotion	Levomenthol 1.4 % w/v | Camphor 0.6 % w/v | Acetylsalicylic Acid 1.2 % w/v | Methyl Salicylate 0.6 % w/v	M02AC	No	Diethylamine Salicylate | Heparin Sodium | Menthol (M02AC) Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)
Movelat Relief	Mucopolysaccharide	M02AC	No	Diethylamine

Gel	Polysulfuric Acid Ester 0.2 % w/w | Salicylic Acid 2 % w/w			Salicylate | Heparin Sodium | Menthol (M02AC) Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)
Movelat Cream	Mucopolysaccharide Polysulfuric Acid Ester 0.2 % w/w | Salicylic Acid 2 % w/w	M02AC	No	Diethylamine Salicylate | Heparin Sodium | Menthol (M02AC) Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)
Bell's Wintergreen Ointment	Cajuput Oil 0.12 % w/v | Eucalyptus Oil 1 % w/v | Methyl Salicylate 9 % w/v |	M02AC	No	Diethylamine Salicylate | Heparin Sodium | Menthol (M02AC)

	Menthol 0.5 % w/v			Methyl Nicotinate | Hydroxyethyl Salicylate | Methyl Salicylate | Ethyl Salicylate (M02AC)

Appendix 5: Medicines with ATC Code D that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Wasp-Eze	Benzocaine 1 % w/w | Mepyramine Maleate 0.5 % w/w	D04AB04	No	Promethazine Hydrochloride (D04AA10) Dimetindene Maleate (D04AA13) Chlorphenoxamine Hydrochloride (D04AA34)
Burneze Spray	Benzocaine 1 % w/w	D04AB04	No	Promethazine Hydrochloride (D04AA10) Dimetindene Maleate (D04AA13) Chlorphenoxamine Hydrochloride (D04AA34)
Eurax Cream	Crotamiton 100	D04AX	Yes	

	mg/g			
Hemocane Cream	Benzoic Acid 0.4 % w/w | Cinnamic Acid 0.45 % w/w | Bismuth Oxide 2 % w/w | Zinc Oxide 10 % w/w | Lidocaine Hydrochloride 0.65 % w/w	D04AX	No	Promethazine Hydrochloride (D04AA10) Dimetindene Maleate (D04AA13) Chlorphenoxamine Hydrochloride (D04AA34)
Tea Tree and Witch Hazel Cream	Camphor 0.52 % w/w | Hamamelis Virginiana 40.61 % w/w | Eucalyptus Oil 1.04 % w/w | Zinc Oxide 3.11 % w/w | Methyl Salicylate 1.04 % w/w | Melaleuca Oil 2.5 % w/w	D08AX	No	Propan-1-ol | Propan-2-ol | Mecetroniumetilsulfate (D08AX53)
Bismuth Subnitrate and	Bismuth Subnitrate 20 % w/w |	D09AA13	Yes	

Iodoform Paste Impregnated Gauze	Iodoform 40 % w/w | Liquid Paraffin 40 % w/w			
Isotrex Gel	Isotretinoin 0.05 % w/w	D10AD04	No	Adapalene (D10AD03) Tretinoin (D10AD01) Trifarotene (D10AD06)
Brevoxyl	Benzoyl Peroxide 4 % w/w	D10AE01		Trifarotene (D10AD06)
Toctino 10mg Soft Capsules	Alitretinoin 10 mg	D11AH04	No	Pimecrolimus (D11AH02)
Toctino 30mg Soft Capsules	Alitretinoin 30 mg	D11AH04	No	Pimecrolimus (D11AH02)

Appendix 6: Medicines with ATC Code C that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Dibenyline Capsules 10mg	Phenoxybenzamine Hydrochloride 10 mg	C04AX02	No	Phentolamine Mesilate (C04AB01)
Oily Phenol Injection 5% w/v	Phenol 50 mg/mL	C05BB05	Yes	
Venoruton 2% Gel	O-(Beta-Hydroxyethyl)-Rutosides 2 g	C05CA54	No	Diosmin | Hesperidin (C05CA53)
Lercanidipine Hydrochloride 10mg Film-coated Tablets	Lercanidipine Hydrochloride 10 mg	C08CA13	No	Amlodipine (C08CA01) Felodipine (C08CA02) Nifedipine (C08CA05) Nimodipine (C08CA06) Lacidipine (C08CA09)
Lercanidipine Hydrochloride 20mg Film-coated Tablets	Lercanidipine Hydrochloride 20 mg	C08CA13	No	Amlodipine (C08CA01) Felodipine (C08CA02) Nifedipine (C08CA05)

				Nimodipine (C08CA06) Lacidipine (C08CA09)
Inegy 10mg/10mg Tablets	Ezetimibe 10 mg | Simvastatin 10 mg	C10BA02	No	Atorvastatin| Ezetimibe (C10BA05) Rosuvastatin | Ezetimide (C10BA06)
Inegy 10mg/20mg Tablets	Ezetimibe 10 mg | Simvastatin 20 mg	C10BA02	No	Atorvastatin| Ezetimibe (C10BA05) Rosuvastatin | Ezetimide (C10BA06)
Inegy 10mg/40mg Tablets	Ezetimibe 10 mg | Simvastatin 40 mg	C10BA02	No	Atorvastatin| Ezetimibe (C10BA05) Rosuvastatin | Ezetimide (C10BA06)
Inegy 10mg/80mg Tablets	Ezetimibe 10 mg | Simvastatin 80 mg	C10BA02	No	Atorvastatin| Ezetimibe (C10BA05) Rosuvastatin |

				Ezetimide (C10BA06)

Appendix 7: Medicines with ATC Code A that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Corsodyl Dental Gel	Chlorhexidine Gluconate 1 % w/w	A01AB03	No	Hexetidine (A01AB12) Benzydamine (A01AD02)
Corsodyl Mint Mouthwash	Chlorhexidine Digluconate 0.2 % w/v	A01AB03	No	Hexetidine (A01AB12) Benzydamine (A01AD02)
Phillips Milk of Magnesia	Magnesium Hydroxide 415 mg/5 mL	A02AA04	Yes	
Fybogel Mebeverine	Isphagula Husks 3.5 g| Mebeverine Hydrochloride 135 mg	A03AA04	No	Mebeverine (A03AA04) Isphaghula Husks (A06AC01)
Dual Lax Extra Strong Coated Tablets	Cascara 130 mg | Aloin 10 mg | Senna Leaf 32 mg	A06AB	No	Charcoal | Senna Leaf | Sulfur | Rhubarb Extract (A06AB06) Bisacodyl (A06AB02) Isphaghula Husks (A06AC01)

				Sennosides (A06AB06) Sodium Picosulfate | Magnesium Oxide | Citric Acid Anhydrous (A06AB58)
Ca-C 1000 Sandoz	Calcium Carbonate 0.327 g | Calcium Lactogluconate 1 g | Ascorbic Acid 1 g	A11GB01	No	Ascorbic Acid | Sodium Ascorbate (A11GA) Calcium Carbonate (A12AA04)
Dalivit	Ergocalciferol 400 IU | Ascorbic Acid 50 mg | Nicotinamide 5 mg | Thiamine Hydrochloride 1 mg | Pyridoxine Hydrochloride 500 mcg | Retinol Palmiitate 5000 IU | Riboflavin 400 mcg	A11JA	No	Thiamine | Pyridoxine | Cyanocobalamin (A11DB) Riboflavin | Thiamine | Nicotinamide| Pyridoxine | Ascorbic Acid (A11EB) Ergocalciferol | Dl-Alfa-Tocopheryl Acetate | Retinol (B05XB)
Woodward's	Dill Seed Oil	A16A	No	Simethicone (A03AX13)

Gripe Water - Alcohol Free & Sugar Free	Terpnenless 2.3 mg/5 mL | Sodium Hydrogen Carbonate 52.5 mg/5 mL			

Appendix 8: Medicines with ATC Code R that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
AAA Sore Throat Spray	Benzocaine 1.5 mg/dose	R02AD01	No	Lidocaine Hydrochloride | Alum | Propyl Hydroxybenzoate (R02AD02)
Accolate 20mg	Zafirlukast 20 mg	R03DC01	No	Montelukast (R03DC03)
Covonia Chesty Cough Mixture Mentholated	Squill Tincture 0.6 mL/5 mL | Levomenthol 4 mg/5 mL | Liquorice Liquid Extract 0.125 mL/5 mL	R05C	No	Bromhexine Hydrochloride (R05CB02) Ambroxol Hydrochloride (R05CB06) Hedera Helix Extract (R05CA)
Menthodex Cough Mixture	Ammonium Chloride 100 mg/5 mL | Tolu Tincture 0.001 mL/5 mL | Tussilago	R05CA	No	Sodium Citrate | Guaifenesin | Methoxyphenamine Hydrochloride

	Farfara 0.0004 mL/5 miL | Marrubium Vulgare 0.0015 mL/5 mL | Menthol 7.75 mg/5 mL | Sodium Citrate 50 mL/5 mL | Squill Tincture 0.001 mL/5 mL			(R05CA03) Hedera Helix Extract (R05CA)
Cofsed Linctus	Chlorphenamine Maleate 2 mg/5 mL | Pholocodine 5 mg/5 mL | Ephedrine Hydrochloride 8 mg/5 mL	R05DA08	No	Dextromethorphan Hydrobromide (R05DA09)
Baby Meltus Cough Linctus	Acetic Acid 0.42 mL/5 mL	R05DB	No	Dextromethorphan Hydrobromide (R05DA09)
Numark Chesty Cough Expectorant	Ammonium Chloride 130 mg/5 mL | Diphenhydramine Hydrochloride 14 mg/5 mL	R05F	No	Triprolidine Hydrochloride | Guaifenesin | Dextromethirphan Hydrobromide |

				Pseudoephedrine Hydrochloride (R05FA02)
Friars Balsam BP	Sumatra Benzoin 10 % w/v | Storax 10 % w/v	R05X	No	Peppermint Oil | Cajuput Oil | Eucalyptus Oil | Clove Oil | Methyl Salicylate | Juniper Berry Oil | Levomenthol (R05X)
Benadryl Allergy Relief	Acrivastine 8 mg	R06AX18	No	Loratadine (R06AX13)

Appendix 9: Medicines with ATC Code N that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Librium 5 mg Capsules	Chlordiazepoxide Hydrochloride 5 mg	N05BA02	No	Bromazepam (N05BA08) Lorazepam (N05BA06) Diazepam (N05BA01) Clobazam (N05BA09)
Kalms Tablets	Gentian 22.5 mg | Humulus Lupulus 45 mg | Valeriana Officinalis 33.75 mg	N05CM	No	Diphenhydramine Hydrochloride (N05CM)
Quiet Life Tablets	Passiflora Incarnata 58 mg | Humulus Lupulus 75 mg | Valeriana Officinalis 50 mg | Lactuca Virosa 29 mg | Leonurus Cardiaca 34 mg	N05CM	No	Diphenhydramine Hydrochloride (N05CM)

Appendix 10: Medicines with ATC Code D that have no available Authorized Marketing Authorization

Medicine Name	Active Ingredient	ATC Code	Article 20	Therapeutic Substitute
Scholl Athlete's Foot Powder	Tolnaftate 1 % w/w	D01AE18	No	Terbinafine Hydrochloride (D01AE15) Amorolfine (D01AE16) Ciclopirox Olamine (D01AE14)
Scholl Athlete's Foot Spray Liquid	Tolnaftate 0.068 % w/w	D01AE18	No	Terbinafine Hydrochloride (D01AE15) Amorolfine (D01AE16) Ciclopirox Olamine (D01AE14)
Metanium Nappy Rash Ointment 20 & 5 & 3 % w/w	Titanium Dioxide 20.0 % w/w | Titanium Peroxide 5.0 % w/w |	D02	No	Benzyl Alcohol | Benzyl Benzoate | Benzyl Cinnamate | Zinc Oxide | Lanolin

	Titanium Salicylate 3.0 % w/w			(D02AB)
Calamine Lotion BP	Zinc Oxide 5 % w/v | Calamine 15 % w/v	D02AB	No	Zinc Oxide | Benzyl Alcohol | Benzyl Benzoate | Benzyl Cinnamate | Lanolin (D02AB)

Appendix 11: Summary of recurring ideas and codes

Interview Extract	Codes	Theme
The fees for the applications and reapplications is an additional cost.	Increase expenses in importing medicines	**Financial costs**
Some of the alternatives available are have a higher price. It may not be much but it adds up.	Rise in prices of available medicines	
We did not have to spend on repackaging and relabeling since the medicines are in English.	Increase expenses in importing medicines	
Sourcing from the UK was cheaper in the sense that there were established shipping deals compared to having to negotiate new ones from new suppliers in other EU countries.	Increase expenses in importing medicines	
Medicines not available can delay patient treatment and prolong their hospital stay.	Patients pay more	
When treatment has to be shifted it could have additional cost to the patient.	Patients pay more	
Authorities were doing their best but obviously this is not something that happens often.	Unfamiliar scenario	**Brexit is an unprecedented event**
As far as I know, Brexit is a quite a bit of	Unfamiliar scenario	

a unique experience. *With Brexit, stakeholders can plan well but cannot perfectly see how the events would unfold.* *The protocols moving forward are untested. It's more we see how this goes and adjust.* *This is like a first time for everyone. It feels like an experiment that can really affect a lot of people in real time.*	Uncertainty of consequences Uncertainty of consequences Unfamiliar scenario	
Some patient's would rather not buy when they cannot find the brand they prefer. *Patients have gotten used to a certain brand that it is a household name and do not think that other medicines that are similar work as effectively.* *Sometimes marketing a product is not cost-effective as the public would not respond well to it.* *I have clients who refuse to try a different brand because that is not what the doctor prescribe. It's a bit hard to try to convince them.*	Patient's preference Patient's preference Alternative hesitancy Alternative hesitancy Alternative hesitancy	**Public's attitude with medicines**

When we introduce an alternative in the market there is additional effort to market it, to make the public aware and to get them to trust the product. It takes time. It is not something instant.	Alternative hesitancy	