# Pharmaceutical Regulation, Policy and Access to Medicines

LILIAN WISMAYER

*Submitted in fulfilment*

*of the requirements of the*

*degree of Doctor of Philosophy*

Department of Pharmacy

University of Malta

2023

L-Università ta' Malta

**University of Malta Library – Electronic Thesis & Dissertations (ETD) Repository**

The copyright of this thesis/dissertation belongs to the author. The author's rights in respect of this work are as defined by the Copyright Act (Chapter 415) of the Laws of Malta or as modified by any successive legislation.

Users may access this full-text thesis/dissertation and can make use of the information contained in accordance with the Copyright Act provided that the author must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the prior permission of the copyright holder.

“At last, the era of cures is upon us.

Be careful what you wish for.”

(Husereau and Reed, 2019)

*Dedicated to my family.*

# Acknowledgments

I would like to express my sincere appreciation towards my supervisors, Prof Lilian Azzopardi and Dr Maurice Zarb Adami, for their counsel and encouragement throughout this research.

I am grateful to numerous stakeholders who contributed their time and invaluable input, and who participated so enthusiastically in this research.

I also acknowledge the staff at the University of Malta for their assistance.

I would especially like to show my appreciation to my family for their unwavering encouragement and constant support.

# Abstract

Access to Medicines has become core to the European debate. Whilst complex legislation targets medicines' quality, safety and efficacy, patients experience disparate levels of access to these therapies. Paradigms for improvement mainly focus on an individual barrier. This study looked beyond standard, isolated criteria and explored access determinants in the wider and dynamic health system context, by addressing following research aims.

- To identify and evaluate factors which may impact on Access to Medicines.
- To propose methodologies which enable sound decision-making strategies to be adopted in the area of Access to Medicines.

Using primarily qualitative techniques, stakeholders' perceptions of barriers to medicines' access were investigated and the influence of policy and regulation examined. A systematic mixed-method, step-wise approach was adopted with each stage of study informing the next. The results of a literature review, and unstructured interviews and questionnaires with health care professionals, were used to design semi-structured interviews seeking experts' perspectives on health care provision, payer advocacy, health economics, pharmaceutical policy and regulation. A focus group was used to consolidate and validate the study proposals.

The findings demonstrate that more concerted and concrete action is necessary at Member State and European Union level. Deterrents to medicines' access are entrenched and often replicated at various health system strata. The results endorse the need for a tool-kit which seamlessly bridges regulatory and health care needs. Through the identification of core

determinants, a supportive framework coordinated at European level was developed to evidence and optimise medicines' access. It enables Member States to adopt a transparent, cohesive and documented national policy which explicitly upholds Access to Medicines and provides direction towards fostering this goal. Whilst allowing for country-specific customisation, the gradual realisation of the framework can facilitate progressive harmonisation of scientific norms and processes.

The access framework developed through this study creates an integrated evaluation cycle embedded in European health systems, streamlining best-practice guidelines to medicines' access.

**Keywords**

Access to Medicines, Policy, Regulation, Health Systems, Framework

# Table of Contents

# List of Figures



# List of Tables

# List of Acronyms

| | |
|---|---|
| ATM | Access to Medicines |
| CAR | Chimeric Antigen Receptor |
| CHMP | Committee for Medicinal Products for Human Use |
| DTC | Drugs and Therapeutics Committee |
| EC | European Commission |
| EDQM | European Directorate for the Quality of Medicines & HealthCare |
| efpia | European Federation of Pharmaceutical Industries and Associations |
| EMA | European Medicines Agency |
| EPR | External Price Referencing |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| EUnetHTA | European Network for Health Technology Assessments |
| FMD | Falsified Medicines Directive |
| GDP | Gross Domestic Product |
| HMA | Heads of Medicines Agencies |
| HTA | Health Technology Assessment |
| NCA | National Competent Authority |
| NCE | New Chemical Entity |
| NHS | National Health System |
| NMP | National Medicines Policy |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| RWD | Real World Data |
| RWE | Real World Evidence |
| SmPC | Summary of Product Characteristics |
| WHO | World Health Organization |

# Chapter 1: Introduction

## 1.1 Access To Medicines

Access to appropriate health care, including medicines, is regarded as an established fundamental human right and governmental responsibility (Perehudoff and Forman, 2019). Access to health services has been referred to as the "timely use of services according to need" (Campbell et al., 2000). More specifically, Access to Medicines (ATM) has been described as ensuring that medicines of an appropriate quality are available at all times, at an affordable price, within the context of a functioning health system (Bigdeli et al., 2018). In highly developed countries, access to essential medicines is a right enforceable at law and restrictions in this regard have been successfully challenged in the courts (Hogerzeil et al., 2006).

Human rights have the power to radically transform the social and legal climate for improved medicines' access (Forman, 2008). In turn legislation and policy are powerful tools which can significantly support equitable access to health services and treatments. The literature attests to the importance of the legal infrastructure which has the ability to change environments, enabling access to medical services and medicines (Vargas-Peláez et al., 2014). This legal architecture includes legislation and regulation as well as policies (Burris et al., 2010; Clarke et al., 2016). Indeed a number of countries adopt regulation with core obligations which serve as a foundation to the right to health (Perehudoff and Forman, 2019) and which explicitly includes a mandate for access to health services or more specifically to medicines (Perehudoff et al., 2006). National medicines' policies can further this commitment, complementing legislation in more detailed and dynamic guidance associated

to the evolving health care scenario (Perehudoff, 2020). The complex legal infrastructure defined in the European Union (EU) strongly impacts ATM across the Member States, as well as in other countries (Perehudoff et al., 2021).

Whilst legislation and policy are fundamental determinants of ATM, other considerations include: the increasing cost of these therapies[1] (Henshall et al., 2011), intellectual property rights and research and development (Krikorian and Torreele, 2021), the availability of pertinent, adequate information (Bigdeli et al., 2018), whether the appropriate product is available to patients, its rational use, as well as the health care and reimbursement model and market characteristics (Jongh et al., 2021). Social policy also plays a part, particularly in the context of patient mobility across the EU, since the free movement of people cannot exclude patients who wish to take advantage of this freedom (Bertinato et al., 2005). As a result, a legislative infrastructure addressing cross-border health care and pharmaceuticals[2] has developed which has been supplemented by a number of European Court of Justice Rulings ( Paulus et al., 2002; Sieveking, 2007). This is a still-evolving scenario with each ruling raising questions of interpretation and threatening the delicate balance between internal market legislation, the European regulatory framework and national competence. This has served to further highlight the diversified characteristics of the Member States' pharmaceutical markets impacting on patients' ATM.

[1] World Health Organisation (WHO). The Global Health Observatory (GHO): Median consumer price ratio of selected medicines [Internet]. 2022 [cited 2022 Dec 12]. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/11

[2]Council Regulations. Decision No 204 of 6th October 2005 (EEC) No. 1408/71 and (EEC) No 574/72 of the Council of 14 June 1971 on the application of social security schemes to employed persons, to self-employed persons and to members of their family moving within the Community, under which it is the duty of the Administrative Commission to deal with all administrative matters arising from Regulation (EEC) No 1408/71 and subsequent regulations [Internet]. Official Journal of the European Union 2006; L 254/1 [cited 12th Nov 2022]. Available from: http://eur-lex.europa.eu/eli/dec/2006/613(1)/oj

The net result of these aspects and their variation in practice in the different Member States is one of pan-European inequities and inequalities in medicines' access (Jongh et al., 2021). In 2017, the European Parliament passed a resolution (2016/2057[INI]) expressing concern at this situation and calling for action aimed at improving ATM[3]. The Pharmaceutical Strategy for Europe[4], launched by the European Commission (EC) in 2020, also contributes to Europe's Beating Cancer Plan[5]. Amongst other objectives, both seek to boost innovative medicines' development, prioritise unmet medical needs and improve patient ATM. A better elucidation and understanding of the factors which prevail in this scenario would contribute greatly towards this goal.

Paradigms for improving ATM most often focus on the individual barrier or cause and do not relate to the wider perspective, which is generally dynamic, complex and rooted in a particular context (Bigdeli et al., 2013a).

## 1.2 The European Pharmaceutical Infrastructure

Scientific advances over the last century have presented both opportunities as well as challenges in the health care arena, as well as in the wide-ranging therapeutic options available to extend our lifespan and improve our quality of life. This has necessitated a need

[3] European Parliament. European Parliament resolution of 2 March 2017 on EU options for improving access to medicines (2106/2057(INI)) [Internet]. March 2017 [cited 2021 Mar 26]. Available from: https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN.html

[4] European Commission. Pharmaceutical Strategy for Europe (2020) [Internet]. 2020 [cited 2021 Mar 21]. Available from: https://health.ec.europa.eu/publications/pharmaceutical-strategy-europe_en

[5] European Commission. Europe's Beating Cancer Plan. Communication from the commission to the European Parliament and the Council [Internet]. February 2022 [cited 2023 Jan 24]. Available from: https://health.ec.europa.eu/system/files/2022-02/eu_cancer-plan_en_0.pdf

to regulate the products used for this purpose, predominately medicines, stimulating the development of pharmaceutical regulatory sciences and a unique model of regulation in the EU (Pignatti et al., 2004).

The primary objective of the European pharmaceutical regulatory system is to ensure that, prior to allowing them to be placed on the market, medicinal products are of an approved level of quality, safety and efficacy[6]. These aspects are proactively monitored for as long as the product remains available and data in this regard continues to be generated throughout the medicine's lifecycle. The product's marketing authorisation is based on a benefit-risk assessment in light of its context of use and approved indications[7]. Appropriate information is made available to patients and health care professionals in order to advocate the medicines' rational use[8]. Consequently, European medicines' regulation aims to cover the product's lifecycle in its entirety, from research and development to manufacture and distribution, including pharmacovigilance. To achieve this objective, a highly sophisticated legislative infrastructure has evolved since the inception of the first European directive in 1965 (Pignatti et al., 2004). This is upheld by a complex network of national medicines competent authorities from the Member States of the EU and the European Economic Area (EEA) who work together in an increasingly integrated and harmonised fashion[9]. They can draw on the

[6] European Commission. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, Official Journal of the European Communities, No. 022 , 09/02/1965 P. 0369 – 037 [Internet] official Journal of the European Communities 1965 [cited 2021 Oct 15]. Available from: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31965L0065:EN:HTML

[7] European Medicines Agency (EMA). Committees [Internet]. December 2013 [cited 2021 Mar 21]. Available from: https://www.ema.europa.eu/en/committees/how-committees-work

[8] European Medicines Agency (EMA). Product-information requirements [Internet]. No date [cited 2021 Mar 21]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information-requirements

[9] European Medicines Agency (EMA). European medicines regulatory network [Internet]. No date [cited 2022 Dec 12]. Available from: https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network

opinions and advice of thousands of experts throughout the EU and are supported by a number of organisations such as the European Directorate for the Quality of Medicines & Health Care (EDQM) of the Council of Europe[10]. They are united in the Heads of Medicines Agencies (HMA) and coordinated by the European Medicines Agency (EMA)[11]. As a result, the knowledge and expertise harnessed by the National Competent Authorities (NCAs) is channelled into a myriad of scientific committees, working parties and expert groups such as the Committee for Medicinal Products for Human Use (CHMP), the Pharmacovigilance Risk Assessment Committee (PRAC), the Pharmacogenomics Working Party, the Geriatric Expert Group, and many others[7]. The HMA has the remit to establish strategy and ensure harmonisation of the regulatory network[12]. It works in tandem with the EC and the EMA to make maximal use of pan-European resources in order to ensure effective operation and best practice in this field.

The EU pharmaceutical regulatory model targets the highest standards in the quality, safety and efficacy of medicines made available to a population exceeding 500 million (globally the third largest), as well as countless other patients across the world who have access to these products. The backbone of this model takes the form of the large body of legislation collated in EudraLex[13] which incorporates the EU rules and regulations governing the entire life span of a medicinal product. The major intent inherent in EudraLex is that of protecting

[10] Council of Europe. Council of Europe Portal: European Directorate for the Quality of Medicines & Healthcare [Internet]. No date [cited 20th May 2020]. Available from: https://www.edqm.eu

[11] European Medicines Agency (EMA). What we do: Authorization of Medicines. London, European Medicines Agency [Internet]. February 2020 [cited 2020 Jul 16]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

[12] Heads of Medicines Agencies (HMA). About HMA [Internet]. No date [cited 2021 Mar 20]. Available from: https://www.hma.eu/

[13] European Commission. Public Health. EudraLex - EU Legislation. [Internet]. No date [cited 2021 Oct 2]. Available from: https://health.ec.europa.eu/medicinal-products/eudralex_en

public health by ensuring that only effective medicines of the appropriate quality are available on the market (Mossialos et al., 2004). It also fosters a collaborative and coordinated approach in areas such as emergency management, blood products and vaccines, and in addressing challenges presented by disorders such as dementia which will only grow in the future. On the other hand, the founding principles of the EU compel it to safeguard and, wherever possible promote, liberal trade and the efficient and effective functioning of the internal market. This inexorably leads to a need to bolster a vibrant pharmaceutical industry and to champion innovation in this sector. The EC therefore adopts the dual objective of safeguarding public health whilst supporting a competitive industry crucial to the European economy. This industry generates an approximate 20% return with over €100 billion trade surplus[14], is responsible for over 800,000 employees and has a significant spill-over effect into the economy[15].

These rules, intended to achieve the highest level of patient protection, may unintentionally produce other impacts, some of which are neither apparent immediately nor understood in the long-term. This is illustrated by the Falsified Medicines Directive (FMD)[16] which came into force in February 2019. There can be no denying that the danger of falsified medicines infiltrating the legal supply chain constitutes a global threat with a significant political

[14] Eurostat. Statistics Explained. International trade in medicinal and pharmaceutical products [Internet]. 2022 March [cited 2023 Feb 22]. Available from: https://ec/europa/eu/eurostat/statistics_explained/index.php?title=International_trade_in_medicinal_and_pharmaceutical_products#An_increasing_trade_surplus

[15] European Parliament. Report on EU options for improving access to medicines (2016/2057(INI)) Committee on the Environment, Public Health and Food Safety [Internet]. 2017 February [cited 2021 Oct 22]. Available from: http://www.europarl.europa.eu/doceo/document/A-8-2017-0040_EN.html

[16] European Commission. Directive 2011/62/EU of the European Parliament and of the Council amending Directive 2011/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products [Internet]. Official Journal of the European Union 2011 [cited 2021 Nov 15]. Available from: https://eur-lex.europa.eu/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF

dimension and obvious implications to patients and the bona-fide industry. It is exacerbated by a rise in the online retail of medicines from unauthorised sources difficult to control through standard enforcement mechanisms. Although the actual quantum of the problem cannot be precisely determined it has been estimated that it is costing the EU €10.2 billion annually, replaces 4.4% of legitimate sales, results in a substantial job loss and represents a reduction in government revenue of €1.7 billion annually[17]. The FMD aims to counter this hazard through a Delegated Act which addresses the consolidation of the legal supply chain, internet pharmacies and a system which detects falsified medicines. Over 10 billion packs dispensed throughout the EU annually must now be serialised allowing electronic verification of their authenticity. Wholesalers and pharmacies are required to operate this system which will have to be seamlessly integrated into their workflow. The choice of a Delegated Act as the legislative tool for adoption makes the implementation of content, timeline and methodology identical in all the Member States, with no flexibility in the transposition into national law. Whilst the benefits of this legislation are incontrovertible, its complexity and the investment and costs it brings with it are colossal. These will inevitably be passed on to consumers and ironically, legislation intended to increase patient safety may reduce medicines' access.

Hodges et al (Dalton et al., 2022) investigated how implementation of the FMD impacted community pharmacies. They found that besides financial consequences (hardware, software and increased workload), time with patients and dispensing practice were negatively

[17] European Union Intellectual Property Office (EUIPO). €10.2 billion lost every year across the EU due to fake medicines. Press Release, September 29, 2016 [Internet]. September 2016 [cited 2021 Nov 15]. Available from: https://euipo.europa.eu/tunnel-web/secure/webdav/guest/document_library/observatory/resources/research-and-studies/ip_infringement/study9/Press_release-pharmaceutical_sector_en.pdf

influenced. Another study on hospital pharmacies also identified financial implications and a notable increase in cumulative workload, as well as an impact on the supply chain resulting in drug shortages (Fittler et al., 2020). Merks et al (Merks et al., 2022) focused on how the supply chain has been affected, revealing operational restructuring and high implementation costs within a context of financial restrictions in health care delivery, with negative implications on drug budgets.

A similar currently emerging aspect is that of environmentally sustainable medicines. Besides social and governance issues, the pharmaceutical sector is today being encouraged to incorporate environmental performance. The EC, in its Pharmaceutical Strategy[18], describes the actions necessary to improve the environmental sustainability of medicines in the EU. This has the laudable objective of introducing measures throughout the product's lifecycle aimed at minimising the entry of pharmaceutical residues into the environment. Like the FMD, these will almost certainly indirectly affect medicines' access. The challenge is to protect public health through greener medicines whilst ensuring their equitable access (Moermond et al., 2022).

## 1.3 The Pharmaceutical Industry

Understandably, the pharmaceutical industry is significantly different to most other industries. It stands out as the most highly regulated, and the products it manufactures are not

[18] European Commission. Pharmaceutical Strategy for Europe (2020) [Internet]. 2020 [cited 2021 Jun 14]. Available from: https://health.ec.europa.eu/publications/pharmaceutical-strategy-europe_en

subject to the market forces generally brought to bear in a liberal market. These relatively expensive products are vital necessities prescribed by health care practitioners for patients who do not have sufficient knowledge to decide which medication is most appropriate for their condition. Governments which espouse the right to health (Gunn and Masellis, 1978) have adopted an approach which not only regulates medicines but also takes responsibility for financing their provision to varying degrees. The specific models ascribed to vary greatly and reflect the perspective of health policy, or more specifically pharmaceutical policy priorities and objectives, embraced by each country (Vogler et al., 2011). As a result, we see disparate mechanisms and extents of price control, cost containment, cost sharing and reimbursement operating in this sector (Mossialos et al., 2006; Kazakov, 2007; Riccaboni et al., 2022). The constantly recurring theme is the challenge faced by policymakers (Kazakov, 2007), as outlined by vice-president Verheugen[19]: that of equilibrating patient access to effective medicines with the ever-increasing burden of pharmaceutical expenditure (Konijn, 2007). Whilst it is undeniable that increased regulation generally translates into higher costs, the European regulatory environment must endeavour to promote and facilitate the development of novel medicinal products which contribute to our health care system. This brings us to the dilemma of costs versus progress in pharmaceutical care.

In the past, the so-called Big Pharma was dominated by European players who were leaders in the development of New Chemical Entities (NCEs) which constituted break-throughs in health care. This scenario has slowly changed, with European companies falling into second place compared to their American counterparts (Gambardella et al., 2000), who succeed in

[19] European Commission. Verheugen, G. Speech/06/547. Delivering better information, better access and better prices. Pharmaceutical Forum Brussels, 29 September 2006 [Internet]. September 2006 [cited 2021 Oct 22]. Available form: https://ec.europa.eu/commission/presscorner/detail/en/SPEECH_06_547

bringing more products to market and in achieving higher profits[20] [21]. Pharmaceutical companies in the EU are also facing intensifying competition from Asia. Citing its steadily weakening competitive position, the European Federation of Pharmaceutical Industries (efpia) points to the need of a more supportive industrial strategy which is concrete in its implementation[22]. Furthermore, it places pharmaceutical strategy in the balance with its industrial counterpart, foreseeing the possibility of the former undermining the latter. At stake in this scenario, is an erosion of Europe's research and development capacity, which will be overtaken by other global players. The EC's outlook, consolidated by the COVID-19 pandemic, has been imbued with a strong sense of caution in terms of its dependence on other world regions [23]. Considering, moreover, that this industry is an undisputed key player of the European economy, the influences it exerts is understandable. There is a negative viewpoint, however, that this influence is used to its advantage prioritising its own commercial interests over health priorities (Abraham and Reed, 2002; Abraham, 2009). A narrative that problems in ATM are 'market failures' leads to a philosophy that mechanisms enabling market access present a solution (Krikorian and Torreele, 2021). This trajectory may propagate a lowering of standards (Davis and Abraham, 2013) and scientific uncertainty (Abraham, 2003).

[20] Lory Gregoire. Gap between EU & US on pharmaceutical investments too wide-industry. Euronews [Internet]. February 2023 [cited 2023 Mar 25]. Available from: https://www.euronews.com/my-europe/2023/02/28/gap-between-eu-us-on-pharmaceutical-investments-too-wide-industry

[21] European Commission. A public-private research initiative to boost the competitiveness of Europe's pharmaceutical industry. Press Release No IP/08/662. 2008.

[22] The European Federation of Pharmaceutical Industries and Associations (efpia). Would the last pharmaceutical investor in Europe pleas turn the lights out? [Internet]. March 2020 [cited 2021 Mar 26]. Available from: https://www.efpia.eu/news-events/the-efpia-view/blog-articles/would-the-last-pharmaceutical-investor-in-europe-please-turn-the-lights-out/

[23] Josep Borell. Why European Strategic Autonomy Matters. European Union External Action [Internet]. March 2020 [cited 2021 May 10]. Available from: https://eeas.europa.eu/headquaters/headquarters-homepage/89865/why-european-strategic-autonomy-matters_en

Moreover, the literature acknowledges a level of failure in the existing system of developing medicinal products, which is marked by a deficit of treatments that truly address health needs (Viergever, 2013; Balasegaram et al., 2015). Whilst the industry can successfully deliver life-changing therapies, many products do not bring significant and/or evidenced benefit. A systematic evaluation by Davis et al (2017) demonstrated that most of the EMA oncology authorisations between 2009 and 2013 had been approved without clear evidence of benefit, either to survival or to quality of life (Davis et al., 2017) There may be a number of reasons why drug development is not health-needs driven (WHO, 2008; Viergever, 2013), but it is difficult to justify such an approach when considering both the cost of the development process, as well as of the products themselves. Any intimation of changing the companies' pricing practice is touted by the industry to be a threat to research and development (Kennedy, 2001; Tobbell, 2009) and is linked to the EU's industrial policy. There is divided opinion in the European Parliament over whether higher medicine's prices lead to greater investment in research [24]. A recent American study by Wouters et al (Wouters et al., 2022) found no correlation between medicines' prices and research investment, both at launch and a year later.

Whilst investing in, and supporting, pharmaceutical innovation is a priority, so is ATM. Both these objectives are ostensibly synergistic but there is inherent difficulty in equilibrating health and industry policy goals, with advocacy for public health exigencies often coming into confrontation with the industry's commercial interests (Morgan et al., 2008; Burci and Gostin, 2017). What the pharmaceutical companies defend as justifiable compensation in a

[24] Tani C. MEPs remain at odds over the EU's new pharma strategy. Science Business [Internet]. 2022 October [cited 2023 Feb 23]. Available from: https://sciencebusiness.net/news/meps-remain-odds-over-eus-new-pharma-strategy

risky business, is often viewed as inimical to equitable medicines' access (Maynard and Cookson, 2001) and is a source of relentless criticism (Hawksbee et al., 2022). There is concern that the profits of the pharmaceutical companies are excessive, leading to increasingly unaffordable therapies (Lindee and Abraham, 1998; Prescrire, 2007). Studies show that this industry generates far higher revenues than other non-pharmaceutical industries, with significantly greater profitability (Ledley et al., 2020; Jonathan and Shimshon, 2021). It is not surprising therefore that there is unabated pressure on governments to reduce the cost of medicinal products (Baker, 2017; Califf and Slavitt, 2019; Asad and Popesko, 2022).

With many health care systems grappling with rising and competing demands for scarce resources and restricted health budgets, tensions rise over medicines' prices (Roughead et al., 2007). Governments have resorted to different negotiating techniques prior to accepting to fund medicinal products. A number of factors determine the outcome, amongst them intellectual property rights, the attractiveness of the market, the health care model, and national medicines' policies which have been shown to influence both pricing and expenditure (Babar et al., 2019). European Member States have implemented different pricing and reimbursement policies but a thorough assessment of this impact on affordable ATM is lacking (Vogler et al., 2017). Launch delay and availability of medicines is correlated and varies substantially across Europe (Danzon et al., 2005; Büssgen and Stargardt, 2022) with interdependent connections between the markets (Danzon and Epstein, 2012). Such policies usually seek to associate the price of the product to the value it brings towards improving public health. It is disheartening to note that less than 5% of new medicinal products have been found to offer breakthrough treatments, with an average of 10% bringing

only modest advantage beyond existing therapies (Lindee and Abraham, 1998; Prescrire, 2007). The literature shows that more research is needed on the wider contemporary challenges facing the European pharmaceutical industry, its interactions with the health system and the value that new medicinal products may bring (Barei, 2018; Sarkis et al., 2021; Asad and Popesko, 2022).

The escalating cost of new medicines has given rise to a demand for more explicit scientific and systematic measurement of their value (Neumann et al., 2015). The value that new technologies may have is a determining feature of ATM (Jönsson et al., 2016) but balancing the positive health outcomes of, for example, novel cancer treatments against their cost is becoming more difficult (Uyl-de Groot et al., 2014). In the pursuit to achieve value-for-money, the tools mostly used by the Member States generally incorporate some form of cost-effectiveness analysis and Health Technology Assessment (HTA) (Uyl-De Groot et al., 2020) which vary between the territories in their application. There are on-going initiatives to address methodological shortcomings and flaws in the value assessment models currently in use. In 2019, Angelis et al. (Angelis et al., 2020) piloted a value assessment tool which evaluated medicinal products used in metastatic castrate-resistant prostate cancer with encouraging results. In 2015, the European Society for Medical Oncology (ESMO) developed a Magnitude of Clinical Benefit Scale (the ESMO-MCBS)[25], since revised in 2017. This scale has the rational of providing a dynamic and unbiased methodology to

[25] ESMO. About the ESMO-MCBS [Internet]. No date [cited 2022 Nov 26]. Available from: https://www.esmo.org/guidelines/esmo-mcbs/about-the-esmo-mcbs#:~:text=About%20the%20ESMO-MCBS%20The%20ESMO-Magnitude%20of%20Clinical%20Benefit,iniquity%20of%20access%20to%20high%20value%20cancer%20treatments

measure a drug's clinical benefit[26]. This value assessment is based on efficacy, toxicity and quality of life data. It also has the intention of promoting accessibility to high-value cancer treatments and of reducing their inequity of access. The scale acts as a guidance tool for prescribers and is also being used as part of HTA. Aside from price negotiations, some form of HTA is commonly used to determine the reimbursement status of the product, but there are notable divergences in its practice across the EU (Vreman et al., 2020). This inevitably results in variations in ATM between the Member States (Cox and Gerard, 2015). It is hoped that future developments by the European Network for Health Technology Assessment (EUnetHTA)[27] will mitigate these divergencies (Ruether et al., 2022). The use of real-world data as a reliable data source in the HTA of pharmaceuticals is also being investigated, both in terms of its acceptability as well as its governance practice (Dsc et al., 2023). A key element is the formulation of a transparent process which translates real-world data into real-world evidence, allowing the valuation of its quality and applicability (Orsini et al., 2020). Further research is being undertaken exploring both the design and analytics of such processes (Capkun et al., 2022) as well as guideline solutions addressing how real-world evidence can inform decisions regarding the entry and utilisation parameters of medicinal products into the health care system (Facey et al., 2020).

The end result of these assessments generally takes the form of positive and negative lists of medicines eligible for reimbursement within the national health system. Pharmaceutical policy should shape the decision-making process which sustains these mechanisms seeking

[26] Jönsson B, Hofmarcher T, Lingdran P, Wilking N. A comparator report on patient access to cancer medicines in Europe revisited Vol 4 IHE Report; Lund, Sweden [Internet]. 2016 [cited 2021 Feb 2021]. Available from: https://www.efpia.eu/media/412110/ihe-report-2016_4_.pdf

[27] EUnetHTA Interntional Projects Office. What are the objectives of Eunet HTA? [Internet]. March 2023 [cited 2023 Mar 15]. Available from: https://www.eunethta.net/

to attain cost-containment, quality of care and improved patient outcomes (Acosta et al., 2014; Belloni et al., 2016). The direction being taken is increasingly evidence-based (Sorenson et al., 2008; Henshall et al., 2011; Carone et al., 2012). It has been proposed that knowledge exchange and transparency should be enhanced to improve the decision-making process (Franken et al., 2012; Panteli et al., 2015). It is recommended that governments continually review policies to rationalise pharmaceutical spending. Rather than aiming at cost-cutting, the objective should be to promote maximal medicines' access for optimal health outcomes by the efficient use of their resources[28].

The notion of incorporating sustainability as a consideration in the financing of pharmaceutical care brings other concerns to the fore (Hollis, 2016; Pani et al., 2016). Member States have enforced different measures to influence cost containment and exert better control on expenditure (Garrison and Towse, 2003; Thomson et al., 2009; Ferrario and Kanavos, 2015; Stadhouders et al., 2016). Moreover, the majority of governments in the EU have adopted a mechanism which caps the price at which a medicine may be sold (Kanavos, 2003). Despite this, the current pan-European diversity in the prices of medicinal products raises uncertainties about affordability and efficient cost containment (Conti and Rosenthal, 2016; Flume et al., 2018). An average 20% of Member States' health budgets is required for the supply of medicines and a major factor implicated in this cost is the ever-increasing price of new medicinal products[29]. This problem is compounded by the fact that such prices diverge

[28] Garcia-Goni M. Rationalizing Pharmaceutical Spending: IMF Working Papers 2022/190 Washington: International Monetary Fund [Internet]. September 2022 [cited 2023 Jan 15]. Available from: https://www.imf.org/-/media/Files/Publications/WP/2022/English/wpiea2022190-print-pdf.ashx

[29] European Parliament. Report on EU options for improving access to medicines (2016/2057(INI)). Committee on the Environment, Public Health and Food Safety [Internet]. February 2017 [cited 2022 Nov 12]. Available from: http://www.europarl.europa.eu/doceo/document/A-8-2017-0040_EN.html

substantially between the Member States (Mrazek, 2002), highlighting that the industry proposes the highest tenable price in a specific market. This renders the product often unaffordable to patients and certainly unsustainable in a number of public health care systems. Whilst budgetary control is essential, even more crucial is the effective allocation of funds such that innovative medication is made available to patients as rapidly as possible (Mills and Kanavos, 2020). Few gains can be made from medicines which have an intrinsically high therapeutic added-value but whose price is too steep for sustainable access into the health care system.

As a result, governments have been faced with mounting pressure to strive for a resolution to this problem, particularly since decisions on pricing and reimbursement fall under the competence of the individual Member States[30]. Their response has been to seek possibilities of European collaboration regarding sharing information on medicines' prices[31], thereby creating the opportunity for coalition negotiations with the industry. In contrast, efpia insists on adhering to confidentiality and upholding current pricing agreements (Michalopoulos, 2016). In the past efpia has been successful in overturning a European restrictive pricing policy. Since the EC's over-riding objective of assuring a liberal market is fundamentally incompatible with instituting profit or price controls, it is likely that this subject will remain a thorny issue for the present. We are, therefore, confronted with the challenge of attaining

[30] European Commission. Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems. Official Journal of the European Communities, No L 40, 11.2.1989, p. 8–11 [Internet]. Official Journal of the European Union 1989 [cited 2021 Oct 24]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31989L0105

[31] Politico. Malta's EU presidency: How it went [Internet]. June 2017 [cited 12th Nov 2022]. Available from: https://www.politico.eu/article/maltas-eu-presidency-how-did-it-go/

the dichotomous objectives of fostering a competitive industry whilst achieving equitable ATM.

## 1.4 Health Systems in Europe

It has been said that the right to health is rendered worthless in the absence of good quality care which is typified by efficiency, resilience, patient-centricity and equitability (Kruk et al., 2018). The United Nations Committee on Economic, Social and Cultural Rights acknowledges the right to the "highest attainable standard of health" and includes acceptability, availability, quality and accessibility in profiling this standard[32]. European Health Systems have traditionally targeted the provision of high-quality care, coupled with equity of access[33]. This has become increasingly challenging over the past decades, with unabated pressure to deliver more and better care with capped or reduced resources. A number of factors have been implicated in destabilising health systems[34] (Guthmuller et al., 2021). Foremost amongst these are an ageing population and population movements which are altering health demographics, and the way in which we address health care needs. Disease patterns are changing as old issues such as tuberculosis re-emerge, and new diseases materialise. Existing disorders are redefined as our understanding of the scientific basis of a number of conditions advances. Anti-microbial resistance threatens to plunge us a century

[32] UN Committee on Economic, Social and Cultural Rights. Substansive issues arising in the implementation of the International Covenent on Economic, Social and Cultural Rights. Geneva: United Nations Economic and Social Council [Internet]. September 2000 [cited 2022 Jul 12]. Available from: https://digitallibrary.un.org/record/647781?ln=en

[33] European Commission.Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01) [Internet]. Official Journal of the European Union 1989 [cited 2021 Oct 24]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX%3A52006XG0622%2801%29

[34] European Commission. Supporting policy with scientific evidence: Shifting Health Challenge [Internet]. September 2022 [cited 2022 Dec 12]. Available from: https://knowledge4policy.ec.europa.eu/shifting-health-challenges_en

backwards in health care (Heads of Medicines Agencies, 2015). A universally acknowledged problem is the plethora of medicinal products from which those deemed essential must be sifted in an effort to contain ever-increasing pharmaceutical costs. Health inequalities and inequity in access-to-care are growing (Guthmuller et al., 2021). These and other similar issues present new public health priorities for which a compelling response is vital unless we are to lose the health gains, we have striven so hard to achieve.

Health system pressures may be a result of megatrends which are currently evident and whose impact is expected to be felt for some time[34]. Ageing or obese populations are an example of such "structural stresses." Other events such as the outbreak of zoonotic diseases, even if foreseen as a forever-present threat, may emerge more suddenly as "acute shocks"[34]. In 2000 the Council of the EU underlined the risk of future challenges, whether in health, societal or macroeconomic, and the need for long-term strategies to address them. This consolidated the principle of instituting policy-driven approaches and re-enforced the notion of sustainability. It also repositioned the criteria of enhanced access to quality care and the need to address inequalities[35]. The concept of health system resilience came about following difficulties in addressing circumstances which tested health care delivery[36]. This led to the premise that health systems' capacity to withstand and recover from shocks and stresses should be fortified to an adequate level of resilience. The European sovereign debt crisis of 2009 incited greater interest in this area. This event put pressure on European health systems (Appleby et

[35] Council Of The European Union. Council conclusions: Towards modern, responsible and sustainable health systems. Luxembourg: Social Policy, Heath & Consumer Affairs Council Meeting [Internet]. June 2011 [cited 2022 Mar 26]. Available: https://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/122395.pdf

[36] European Commission. Assessing the resilience of Health Systems in Europe: An overview of the theory, current practice and strategies for improvement. EU Expert Group on Health System Performance Assessment (HSPA).Publications Office of the EU, Luxembourg [Internet]. 2020 [cited 2022 Mar 26]. Available: https://health.ec.europa.eu/system/files/2021-10/2020_resilience_en_0.pdf

al., 2015; Vogler et al., 2015) eliciting a wide array of policy responses[37], and highlighting susceptibility to economic fluctuations[36]. Similarly, the present war in Ukraine has had a knock-on effect, negatively influencing Member States' ability to finance and deliver health care[38].

The recent coronavirus COVID-19 pandemic also revealed previously unknown, or underestimated innate fragilities (Țăran et al., 2022), amongst them, limitations in the European regulations (Beaussier and Cabane, 2020). The EC has since announced its intention to consider modifications to the pharmaceutical legislation[39]. Additionally, the EMA's mandate has been extended in the interest of public health (Cavaleri et al., 2021). The pandemic also exposed the weaknesses inherent in clinical trials, which are often small, lacking in resources, fragmented and with suboptimal design (Eichler et al., 2020, 2021; Bugin and Woodcock, 2021;). Another point worth noting is that whilst EU regulators worked in tandem to harmoniously authorise vaccines, policy makers reached diverse conclusions on the context of their use (Syn et al., 2016), highlighting the plurality of the Member States' health care models. Such events have strengthened the EC's commitment towards effective, accessible and resilient health systems, which now forms part of the EU agenda on health systems (Wirtz et al., 2017).

[37] Mladovsky P, Srivastava D, Cylus J, Karanikolos M, Evetovists T, Thomson S McKee M. Health policy responses to the financial crises in Europe. Policy Summary 5 (2012) No 5. ISSN 2077-1584. World Health Organization WHO on behalf of the European Observatory on Health Systems and Policies. February 2016 [cited 2022 Oct 18]. Available from: https://www.researchgate.net/publication/265118597_Health_Policy_Responses_to_the_Financial_Crisis_in_Europe/link/56c45a8408aeeffa9e5aa87/download

[38] Borrell J. The ware in Ukraine and its implications for the EU [Internet]. March 2022 [cited 2022 Oct 18]. Available from: https://www.eeas.europa.eu/eeas/war-ukraine-and-its-implications-eu_en

[39] European Commission. Communication on HERA Incubator: Anticipating together the threat of COVID-19 variants. 2021 [cited 2022 Jun 16]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021DC0078

Since accessibility of health care includes ATM (Guthmuller et al., 2021), it would be pertinent to apply the principles of resilience to this area. Consensus is lacking regarding a definition of health system resilience (Abimbola and Topp, 2018; Turenne et al., 2019; Fridell et al., 2020). However, in general terms it can be said to include the ability to identify, prepare for and withstand stresses (Bayntun, 2012; Kruk et al., 2015). The spectrum of stresses may include innovative and expensive medicinal products which will test pharmaceutical care both technically as well as at a macroeconomic level. Using keywords which have been applied to the general context of health systems, it may be surmised that a policy-driven approach should be adopted to develop a long-term strategy optimising access to innovative therapies. In 2019, the Expert Group on Health Systems Performance Assessment (HSPA) conducted a survey on 19 European countries to broadly determine the resilience capacity of their national health systems[36]. This included a number of practical applications showing how the concept may be put into operation in various contexts. One such case which fell under the category of "major shock," described how curative new medicines with proven patient benefit for Hepatitis C can present a significant challenge to the financial stability of health services. In anticipation of stresses of this nature, a number of policy implications should be considered. First and foremost, they should be proactively foreseen and absorbed. This should be followed by adaptation and transformation through system restructuring that ensures improved access and resilience (Burke et al., 2021). In the face of predictable events which may have serious consequences on health care provision, inaction is unacceptable[36].

The rapid evolution of innovative therapies is already placing unprecedented pressure on European health systems heralding new challenges to medicines' access (Jommi et al., 2022).

The advent of personalised treatments offers the potential for superior outcomes (Schuster et al., 2021; Kamdar et al., 2021;  Bishop et al., 2022; Locke et al., 2022) whilst novel clinical approaches have the advantage of improved efficacy and long-term survival (Abramson et al., 2021; Ernst et al., 2021; Jacobson et al., 2021). It is expected that more and more patients may benefit from such transformative therapies, many of which are already in the pipeline (Salmikangas et al., 2015; Barlow et al., 2019) ushering in a new era of pharmaceutical care. However, core barriers to their access are already evident (Simoens et al., 2022) and future resource-intense developments of this nature will test health systems sustainability as never before.

The literature indicates that health care delivery systems have not sufficiently anticipated, and are therefore unprepared for the advent of these breakthrough therapies (Olry de Labry-Lima et al., 2023). There is a clear concern that conventional methodologies of assessing the value they confer on health outcomes are inadequate (Towse and Fenwick, 2019). Caution is advocated regarding a dependence on industry-funded economic evaluations (Olry de Labry-Lima et al., 2023) with studies pointing to limited evidence of the cost-effectiveness of these products (Lloyd-Williams and Hughes, 2021). There are also misgivings about the constraints and pressures that the regulatory assessments of these treatments will bring to bear on policy-makers (Barlow et al., 2019). It is imperative that a novel approach be devised to determine clinical effectiveness (Pearson et al., 2019) of these therapies backed by policies which address their economic and clinical implications (Yeung et al., 2019). This should include monitoring of these long-term effects and the factors influencing survival and relapse of which there is currently limited knowledge (Gribben et al., 2022).

ATM has become core to the European debate (Jönsson et al., 2016) and reducing barriers to medicines' access is a priority for policy-makers across the EU (Jongh et al., 2021). However, in practical terms, it is clear that they face difficulty in contending with this issue (Colbert et al., 2020; Morgan et al., 2020) and in striking a balance between the benefits and costs of novel medicines (Cherny et al., 2016). Policies which can bring about tangible change and which aim at sustainability and universal access, help build resilient health systems[40]. It is recommended that such policies should be designed and implemented at a national level (Jönsson et al., 2016). Considering the scarcity of studies proposing methodologies in this context, it is important that further research be conducted exploring coherent strategies for reforming and building resilience into our systems[40] [41] (Burke et al., 2021) with a focus on ATM.

## 1.5 Health Needs and Essential Medicines

It is lamentable that patients in the EU today do not enjoy equal ATM[42], especially when both the United Nations (United Nations Secretary Generals, 2016), as well as the World Health Organisation[43] acknowledge access to essential medicines as a patient right

[40] Baeten R, Spasova S, Vanhercke B, Coster S; 2018. Inequalities in access to healthcare. A study of national policies. European Social Policy Network (ESPN), Brussels: European Commission. 2018 [cited 2022 Oct 16]. Available from: https://ec.europa.eu/social/BlobServlet?docId=20339&langId=en

[41] European Commission. Assessing the resilience of Health Systems in Europe: An overview of the theory, current practice and strategies for improvement. EU Expert Group on Health System Performance Assessment (HSPA).Publications Office of the EU, Luxembourg [Internet]. 2020 [cited 2022 Mar 26]. Available: https://health.ec.europa.eu/system/files/2021-10/2020_resilience_en_0.pdf

[42] European Commission. Verheugen, G. Speech/06/547. Delivering better information, better access and better prices. Pharmaceutical Forum Brussels, 29 September 2006 [Internet]. September 2006 [cited 2021 Oct 22]. Available form: https://ec.europa.eu/commission/presscorner/detail/en/SPEECH_06_547

[43] World Health Organisation. Access to essential medicines as part of the right to health [Internet]. No date [cited 2021 Dec 3]. Available from: https://www.who.int/health-topics/human-rights#tab=tab_1

(Hogerzeil, 2006). The concept of what is essential is convertible and subject to different contexts (Kar et al., 2010). In its broadest sense it may be deemed to include any product which has the scientifically-proven potential to improve a patient's health. Financial constraints prevent most governments from adopting such an approach and the Transparency Directive[44] allows European Member States to make political choices in this regard. WHO refers to essential medicines as "those that satisfy the priority health care needs of the population"[45], implying the pre-requisite of identifying needs and establishing health priorities. Indicators which guide choices in this regard generally include efficacy, safety, the prevalence of local disease and comparative cost-effectiveness (Wirtz et al., 2017).

The WHO definition of essential medicines has long supported and shaped decision making in the formulation of positive re-imbursement lists at an international level (Quick et al., 2002). It has been shown that high income countries implementing such medicines' lists, in combination with wide-ranging pharmaceutical policy, enable improved access to, and prescribing of effective medication (Duong et al., 2015). However, there is now debate as to whether the WHO definition is being upheld, or indeed whether it is applicable today (Persaud et al., 2019; Hwang et al., 2022), particularly in high-income countries. Current research indicates that policy-makers face difficulty in prioritising high-value medicines (Piggott et al., 2022). Moreover, only approximately 25% of high-income countries operate national medicines lists, often in the ambit of a lack of clear policy (Taglione and Persaud,

[44] European Commission. Directive 2004/109/EC of the European Parliament and of the Council of 15 December 2004 on the harmonisation of transparency requirements in relation to information about issuers whose securities are admitted to trading on a regulated market and amending Directive 2001/34/EC, Official Journal of the European Communities, No L 39038, 31.12.2004. 2004 [cited 2021 Dec 4]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2004.390.01.0038.01.ENG

[45] World Health Organization. Model List of Essential Medicines. 22nd List, 2021. WHO Reference Number: WHO/MHP/HPS/EML/2021.02. September 2021[cited 2022 Mar 20]. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

2021). An examination of listed medicinal products in high income countries reveals the inclusion of therapies associated to both clinical, as well as safety concerns, underscoring problems in the effective selection, or the on-going evaluation of these products (Hogerzeil, 2004; Charles et al., 2019). Ensuring enhanced, timely and equitable ATM is recognised as a primary objective, and research is encouraged on the mechanisms and methodologies which may support this initiative within the EU context (Pace et al., 2013). There is the aspiration that the decision-making process should be based on the effectiveness to public health that the innovative medicine brings, and how this may translate into value for money.

The Commission has recently embarked on a reform of the pharmaceutical legislation to better customise it to modern requirements and challenges[46]. A dominant theme of this revision is directed towards ensuring the timely and equitable access to effective medicinal products by patients in the EU. This should support the extension of the current regulatory obligations of Quality, Safety and Efficacy to Accessibility as a fourth domain. A pan-European decision-making process in this regard would constitute a best-practice approach towards achieving equitable ATM in the EU. Establishing a generic policy based on sound scientific principles is critical to such a harmonised approach. This could take the form of a coherent, transparent and structured methodology, providing stakeholders with the opportunity to obtain a more detailed understanding of the workings of their systems and how they affect ATM. Ultimately the intention should be the determination of appropriate and evidenced decision-making in this context (Haynes, 1999; Hutton et al., 2006). This should help shift resources away from therapies with relatively inferior benefit towards more

[46] European Commission. Frequently Asked Questions: Revision of the Pharmaceutical legislation. April 2023 [cited on 2023 Nov 06]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/qanda_23_1844

cost-effective technologies. Notably, the creation of platforms enabling networking between the Member States is seen as a stepping stone towards more favourable European harmonisation (Hutton et al., 2008). The feasibility of harmonisation between the Member States, and of its benefits and disadvantages in this area, particularly with regard to HTA, remains uncertain (Hutton et al., 2008). The contextual nature of the data which would be generated by the Member States from their different health care models, renders its applicability across multiple territories contentious (Culyer and Lomas, 2006). Any harmonisation process must first achieve consensus at a technical level before progressing to political approval and implementation. The EU's experience in health-related harmonisation initiatives has amply demonstrated that a number of pre-requisites must be in place for such an enterprise to succeed. These include a clearly defined and mutually beneficial objective, the involvement of all stakeholders, a readiness to contribute to the project and a transitional period of collaboration and agreement within a background of extended, open discussion (Hutton et al., 2008). Moreover, whilst the benefits of harmonisation remain questionable, the possibility of inherent disadvantage has also been raised. A major concern would be the adoption of methodologies which are not necessarily fit for purpose in all the Member States (Culyer and Lomas, 2006).

In view of the uncertainties regarding deeper Europeanisation (Dyson, 2002), exploration of its possible disadvantages and benefits in the pharmaceutical arena is necessary. Whilst no definitive meaning to the process of Europeanisation (or "EU-isation") has been established, it can be taken to refer to a re-assignment of organisational policies and procedures (Flockhart, 2010). As a result, there is increased EC influence in the 3 dimensions of politics, policy and domestic policy (or polity) (Borzell and Risse, 2000). The repercussions to this

may differ across Member States, with the possibility of some territories becoming subject to "coercion pressure" (Dyson and Goetz, 2012). The smaller countries in particular have been shown to be more vulnerable to some form of this phenomenon (Azzopardi-Muscat et al., 2016). In terms of pharmaceutical care therefore, it is imperative that the impact of heightened Europeanisation on policy be investigated.

In researching Europeanisation, three typologies of the process have been identified. The first or "bottom-up" approach denotes stakeholders gradually influencing the direction and evolution of policy (Caporaso, 2008), culminating in political development (Howell, 2004). The "top-down" model depicts and EU approach which defines and consolidates decisions which are then incorporated into domestic policies and political structures (Radaelli, 2006). More recent research hypothesises a "circular" approach wherein the "bottom-up" and the "top-down" concepts continually converge and merge (Holzhacker and Haverland, 2006). Such ongoing interaction and co-operation between the EU and domestic levels of governance is described in the literature, highlighting a co-dependence of national and EU institutions (Featherstone and Kazamias, 2000; Howell, 2002). Furthermore, it is postulated that more research exploring the "circular" and iterative process of Europeanisation should be undertaken (Börzel, 2002; Holzhacker and Haverland, 2006) such that its applicability and outcomes be enhanced. It has been observed that research and knowledge regarding Europeanisation in general is poor (Olsen, 2002; Holzinger and Schimmelfennig, 2012) and the literature fragmentary (Wach, 2016). What is certain is that there are undoubted economic implications related to the process[47]. These, in conjunction with other challenges, place the

[47] Ulrich Sedelmeier. Europeanisation in new member and candidate states Living Reviews in European Governance Vol 6 (2011)> Ireg-2011-1 [Internet]. 2011 [cited 2022 Oct 28]. Available from: https://www.europeangovernance-livingreviews.org/Articles/lreg-2011-1/

process of further pharmaceutical Europeanisation at a cross-roads (Warren-jones, 2017) making research in this field vital before an optimal strategy can be configured.

The pharmaceutical industry, which has long clamoured for increased transparency, may also benefit from a pan-European methodology which sustains ATM since this may provide invaluable insight into the deliberative process when making recommendations (Bond et al., 2020). It is recognised that a major factor leading to delays in patient access to effective therapies arises from non-aligned viewpoints and unclear requirements on various aspects relating to lacking or uncertain evidence (Stephens et al., 2012; Moloney et al., 2015; Martinalbo et al., 2016; Ciani et al., 2021). A common approach would support a convergence of understanding leading to improved access to medication which is more closely linked to public health needs (Kim et al., 2019). The identification and assessment of unmet health needs in both international as well as European settings remains a challenge (Manikandan, 2015) which needs to be more pro-actively addressed by policy makers (Allin et al., 2010; Cavalieri, 2013; Smith and Connolly, 2020). The wide variation in understanding the meaning of "needs" is due to the complexity of this concept which is associated to social policy (Reeves et al., 2015; Fiorillo, 2020), health care resources (Fjaer et al., 2017) and which is also dependent on the characteristics of the health care model (Chaupain-Guillot and Guillot, 2015).

As a result, references to "needs assessment" vary extensively (Asadi-Lari et al., 2003) and remain problematic (Hasenclever et al., 2021). This has implications for health care delivery, but despite several proposals, a commonly accepted definition for "needs" remains lacking (Harrison et al., 2013). Responding to unmet needs is intrinsically linked to equitable ATM.

Health policy should define health system needs and incentivise the development of pertinent therapies. The industry should be diverted away from a purely profit-focused approach towards a more patient-oriented one, to better address the patient's best interests. There is an argument for governments to exert more influence into which areas of research should be prioritised, given that medicines are utilised for the public good. Considering the latent potential that science and technology offer today it is unacceptable to witness gaps in addressing disease which could be remedied by more coherent policies.

## 1.6 A Paradigm for Improving Access to Medicines in the European Union

Equity in health care across the EU is a commitment [48] [49] which cannot be achieved in the absence of equitable ATM. In making a case for further research into ATM, one element that stands out is how policies may support, or indeed hamper access, particularly in the context of novel therapies (Bigdeli et al., 2018). National medicines' policies present a sound foundation on which to strengthen ATM[50]. Comprehensive, well-designed and effectively implemented policies can priorities action to scale-up access to therapies with clinically proven benefit. The policy process is, in itself, important since it provides a collaborative opportunity to adapt universal principles to the domestic context (Hoebert et al., 2013). A

[48] Huber M, Stanciole A, Wahlbeck K et al. Quality in and Equality of Access to Healthcare services. European Commission [Internet]. March 2008 [cited 2022 Oct 16]. Available from: https://www.euro.centre.org/downloads/detail/882

[49] Baeten R, Spasova S, Vanhercke B, Coster S; 2018. Inequalities in access to healthcare. A study of national policies. European Social Policy Network (ESPN), Brussels: European Commission. 2018 [cited 2022 Oct 16]. Available from: https://ec.europa.eu/social/BlobServlet?docId=20339&langId=en

[50] Management Sciences for Health. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, VA: Management Sciences for Health, USA Embrey M (Ed.) Part 1: Policy and Economic Issues. Policy and Legal Framework. Chapter 1. Toward sustainable access to medicines [Internet]. March 2012 [cited 2022 Oct 16]. Available from: https://msh.org/wp-content/uploads/2013/04/mds3-ch01-sustainable-access-mar2012.pdf

proposal by the Lancet Commission presents a number of parameters with which to monitor medicines' policies, which include indicators specific to access (Wirtz et al., 2017). The literature endorses the potential role of national policies to improve access to pharmaceutical technologies (Detiček et al., 2018). It has been shown that, generically, access is impacted by the way policies are implemented (Bigdeli et al., 2020). Furthermore, policies may, unintentionally, provoke inequalities in medicines' use (Vogler et al., 2015). Conversely, they may act to reduce unequal medicines' access. It is acknowledged that research is warranted to assess the influence of policies on ATM (Zamora et al., 2019), and how they may be used as a tool for sustainable development in health care (Wirtz et al., 2017).

A failure to recognise and act on the many challenges to medicines' access will have long-term, negative implications on the quality of care delivered to patients. The majority of literature on this topic justly prioritises low- and middle-income countries (Bigdeli et al., 2013b). However, even the richest nations are now struggling with challenges in access to new therapies (Colbert et al., 2020; Morgan et al., 2020). A multi-faceted study on medicinal products for rare diseases demonstrated large variations in access across the EU (Detiček et al., 2018). Another study carried out in the largest five economies in the EU also revealed substantial disparities in access to orphan medicinal products (Zamora et al., 2019). It is clear that, despite all efforts, health inequalities and disparities in medicines' access remain virtually unchanged, persisting both within and between European countries (Eichler et al., 2020, 2021). The case of pan-European divergences in cancer survival, cure-rates and access to new oncologic agents amply attest to this (Appleby et al., 2015; Eichler et al., 2020).

Cancer is a major cause of death globally[51]. In the EU, it is the leading cause of death for patients younger than 65 years old age and the second major cause of death in the older population (Pignatti et al., 2004). Its incidence is rising, with a 21% increase in new cases expected by 2040 compared to 2020[52]. This rate considerably outpaces the expected population growth, therefore multiplying the burden of disease. Simultaneously, cancer care is developing with considerable momentum, with improved diagnostic techniques and novel medicines becoming increasingly available (Wilking and Jönsson, 2005). The EMA has maintained a steadily increasing trend of anti-cancer approvals through the centralised European procedure over the last two decades. Significant progress in cancer treatment and survival rates has been achieved, moving away from cell-toxic, anti-tumour products with severe adverse effects, towards therapies with cell-specific mechanisms of action. Agents targeting cell-signalling pathways have been rapidly followed by immuno-oncologic technologies accompanied by breakthroughs in tumour molecular profiling and precision medicine (Syn et al., 2016; Wilking et al., 2019).

Unfortunately, not all EU patients are able to exploit these advances and the positive health outcomes they confer[53]. The results of a survey conducted in 34 European oncology centres indicate that over 25% of patients with metastatic melanoma lack access to therapy recommended by European treatment guidelines (Kandolf Sekulovic et al., 2017).

[51] Mladovsky P, Srivastava D, Cylus J, Karanikolos M, Evetovists T, Thomson S McKee M. Health policy responses to the financial crises in Europe. Policy Summary 5 (2012) No 5. ISSN 2077-1584. World Health Organization WHO on behalf of the European Observatory on Health Systems and Policies. February 2016 [cited 2022 Oct 18]. Available from: https://www.researchgate.net/publication/265118597_Health_Policy_Responses_to_the_Financial_Crisis_in_Europe/link/56c45a8408aeeffa9e5aa87/download

[52] European Commission. European Cancer Information System: 21% increase in new cancer cases by 2040 [Internet]. March 2022 [cited 2023 Apr 2]. Available from: https://joint-research-centre.ec.europa.eu/jrc-news/european-cancer-information-system-21-increase-new-cancer-cases-2040-2022-03-16_en#:~:text=The%20number%20of%20people%20being,on%20the%20future%20cancer%20burden

[53] Jönsson B, Hofmarcher T, Lingdran P, Wilking N. A comparator report on patient access to cancer medicines in Europe revisisted Vol 4 IHE Report; Lund, Sweden [Internet]. 2016 [cited 2021 Feb 2021]. Available from: https://www.efpia.eu/media/412110/ihe-report-2016_4_.pdf

Furthermore, the study detailed disparities highlighting that access to treatments based on evidenced guidelines is not equal across Europe. An ESMO-led European Consortium study on the accessibility of anti-neoplastic agents in Europe showed similar results for other cancer typologies (Cherny et al., 2016). These findings also revealed significant access inequalities between European countries, particularly to newer therapies for certain types of lung, renal, colorectal, breast and prostate cancers. Although a major criterion of access to cancer therapies in Europe revolves around the different economic strengths of the Member States, other factors are undoubtedly implicated (Costa-Font et al., 2015). A study investigating time-to-access new oncology products in seven high-income Northern European States revealed compelling intra- and inter-country variations (Post et al., 2002).

It is clear that there is no single solution towards mitigating equitable and equal ATM which seemingly goes beyond individual factors such as price (Jönsson et al., 2016). The underlying causes of obstacles to ATM have not been comprehensively researched, are probably multi-factorial and may be interspersed in different components of complex European health care models. They may also emanate from the international dimension (Bigdeli et al., 2018). Bigdeli et al. argue that studies examining ATM should not be restricted to the pharmaceutical sphere but should adopt a wider perspective (Bigdeli et al., 2013a). The literature shows that research on ATM mainly focuses on single demand/supply barriers such as procurement and supply, pricing and cost-recovery mechanisms (Bigdeli et al., 2013a), and fails to explore the wider context of health policy and systems[54]. Albeit important, formulating interventions into individual system components in isolation ignores the inter-

[54] European Commission. Supporting policy with scientific evidence: shifting health challenges [Internet]. September 2022 [cited 2022 Dec 12]. Available from: https://knowledge4policy.ec.europa.eu/shifting-health-challenges_en

linkages inherent in the pharmaceutical and health sector. The consequences are that the outcomes are limited by other system constraints and are usually of a short-term nature (Bigdeli et al., 2013a). It has been posited that research into ATM should look beyond the standard criteria of affordability and availability. It should instead explore access determinants in the fuller context, generating knowledge which informs a more comprehensive understanding of ATM (Panteli et al., 2016). A broader approach, as advocated by the Alliance for Health Policy and Systems Research (Taghreed and De Savigny, 2010), is also in line with the principles of health systems strengthening (Taghreed and De Savigny, 2010). This has the potential to integrate ATM into the wider health care frame of reference with more effective, equitable, enduring and sustainable results. A study in 2019 postulated that multiple causes may be culminating in reduced and unequal access to innovative cancer treatments. It concluded that future research should be fuelled by input and debate from multiple stakeholders, for example regulators, policy-makers, patients and the industry (Wilking et al., 2019).

There is a case for multi-faceted investigations seeking to identify and embed actions for ATM improvement at different system levels. By guiding the formulation of policy, these interventions can be fostered and sustained through such research. The end goal should be incentivising innovation to develop effective therapies for unmet needs, whilst ensuring that patients benefit equitably from these products (Jongh et al., 2021). This research seeks to address the knowledge gaps identified through this review of the literature and within this context, to contribute towards developing a paradigm for equitable ATM in the EU.

## 1.7 Aims and Objectives

Access to appropriate medication is a multi-faceted issue which, unless properly understood and managed, has the potential for grave repercussions to public health. Yet, despite its importance and current relevance, the literature review revealed a number of peritent gaps in key issues related to this topis, as outlined hereunder:

- Obstacles and enablers to medicines' access are not well-understood and studies most commonly focus on single factors such as price, procurement and supply.
- The complex and dynamic relationship between ATM and determinants routed in the wider health perspective has been largely overlooked.
- The influence of pharmaceutical regulation and ATM has not been sufficiently addressed.
- Principally, there exists a slack of scientific methodologies and coherent mechanism promoting ATM.

Considering these gaps, the aim of this research is twofold. The specific research aims are presented hereunder:

**Research Aim 1**: identify and evaluate factors which may impact on Access to Medicines;

**Research Aim 2:** propose methodologies which enable sound decision-making strategies to be adopted in the area of Access to Medicines.

In order to meet the research aims, the following objectives have been developed.

*Objectives associated with Research Aim 1*

**Objective 1A:** to investigate the stakeholders' (health-care professionals, policy-makers, experts and regulators) perceptions of barriers in this area;

**Objective 1B:** to examine and assess how policy may impact on access and sustainability, including market failures; and

**Objective 1C:** to determine how the European legislative infrastructure influences equitable access to medicinal products.

*Objectives associated with Research Aim 2*

**Objective 2A**: to recommend how the balance between the quality of, and access to, medicinal products may be strengthened; and

**Objective 2B:** to propose a framework of measures designed to optimise timely patient access to effective medication.

# Chapter 2: Methodology

## 2.1 Research Design

A detailed literature review provided a pertinent basis for this study, at all stages. The methodology used to ensure a comprehensive review of the literature included the identification of themes dominated by Access to Medicines (ATM), but including the appraisal of complementary topics. The review was undertaken as a continuous process throughout the research period. Reference repositories were scrutinised periodically to ensure the inclusion of the latest material. Moreover, the bibliographies of referenced material were also cross-checked to capture data and ensure that all material has been covered.

Following a thorough, in-depth literature review, methodological triangulation was used to garner data. The factors which have the potential to impact ATM and their rational use, are diverse and complex, and the stakeholders are varied. The methodology, therefore, adopted constituted a mixed-methods approach comprising both quantitative and qualitative components, as advocated by Ryan at al. (2015) and others (Hanson et al., 2005; Almarsdóttir et al., 2014).

Figure 2.1 provides a tabular representation of the research aims and objectives, the stakeholder groups participating in this study, and the research methods adopted to gather data in each phase. A stepwise approach was designed incorporating four main phases of data collection (Malterud, 2001; Flick, 2009; Denzin and Lincoln, 2010). This model enabled data gathered from one phase to inform the next, both in terms of methodology and parameters of investigation.

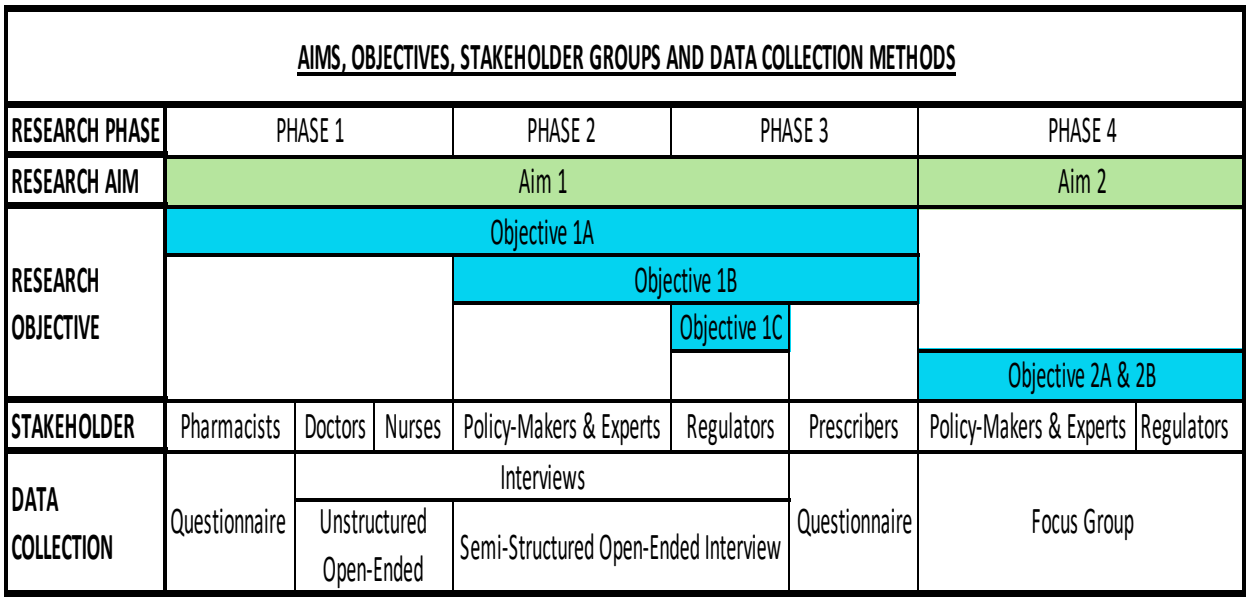


*Figure 2.1: Graphical representation of the research aims and objectives, the stakeholder groups participating in the study, and the data collection methods adopted*

The research tools utilised for this study included structured questionnaires, unstructured and semi-structured interviews and a focus group.

### 2.1.1 Ethics Approval

An overview of the study, including details regarding the proposed methodology, questionnaires and interviews to be used was submitted to the Faculty Research Ethics Committee. Ethics approval was granted (FRECMDS_1920_194-UNIQUE FORM ID:5783_20062020_Lilian Wismayer) and is enclosed in Appendix 1A.

### 2.1.2 Introductory Letter

For all questionnaires and interviews, an invitation letter (Appendix 1B) prepared defining Access to Medicines (ATM) and describing the objectives and context of this study. Each letter was personalised and explained that the participant had been selected due to their experience and expertise in the area. Non respondents were followed up with two reminders, spaced two weeks apart.

## 2.2 Phases of Research

The study comprises four phases. Phases 1, 2 and 3 addressed **Research Aim 1,** as illustrated in Figure 2.1.

*Research Aim 1: To identify and evaluate factors which may impact on Access to Medicines.*

It was important to investigate stakeholders' perceptions of barriers to access. Since this topic is one which embraces many facets, and with wide-reaching consequences, the theoretical stakeholder population is very broad, ranging from patients to politicians, and including various specialities involved in the medical and pharmaceutical fields. For the purposes of this study, the stakeholder cohort incorporated pharmacists, doctors and nurses, directly involved in patient care, as well as experts in policy, finance, health-care provision, pharmaceutical care, and pharmaceutical regulation.

The methodology was designed to incorporate three phases of research. Phase 1 was designed to explore the experiences of health care professionals working closely with patients and their perceptions of barriers to access, and providing a foundation for the next stage of research. Building on the resultant data generated, Phase 2 targeted the identification of major areas or domains which should be addressed when considering ATM. Experts engaged in health care delivery, including medicines' use, Health Technology Assessment (HTA) and pharmaceutical policy contributed to this part of the study. Phase 3 addressed the regulatory overlap with ATM, and in particular how European Union (EU) fora and legislation impact this area.

Phase 4 of the study is intended to address **Research Aim 2**.

*Research Aim 2: propose methodologies which enable sound decision-making strategies to be adopted in the area of Access to Medicines.*

Following evaluation of the data generated during phases 1, 2 and 3, a proposed framework of measures intended to enhance timely access to appropriate medication will be formulated. This will be presented to a focus group incorporating policy-makers and regulators with the intention of validating the model.

## 2.3 Phase 1

The first phase of research had the scope of exploring the work experiences and perceptions of stakeholders engaged in routine health and pharmaceutical care delivery services, namely: pharmacists, medical doctors and nurses. This is in line with Objective 1A.

*Objective 1A: To investigate the stakeholders' perceptions of barriers in this area.*

The research tools adopted in this phase consisted of:

- A structured questionnaire to pharmacists;

Questionnaires are often the tool of choice in medical and pharmacy practice research. They are commonly used to assess pharmacists' perspectives and prescribers' attitudes towards perceived obstacles related to their role (Axelsson et al., 2008; Agomo et al., 2016; Kuipers et al., 2019). The data generated is not compromised by interviewer variability and effects which may yield biased responses. For these reasons, a structured questionnaire was selected as a preliminary data collection tool since it enabled the researcher to gather a large quantity of data efficiently from targeted respondents.

- Unstructured, open-ended interviews to medical doctors and nurses.

The interview is a data gathering technique widely used in both qualitative and quantitative studies (Bryman, 2001). Three predominant forms of research interviews exist: Unstructured Interviews; Semi-Structured Interviews; and Structured Interviews. The former two typologies have distinctive advantages in qualitative research (Kvale, 1996; Waddington and Bull, 2007), and were, therefore selected as research tools in this study.

Unstructured Interviews, used during the first phase of this research, enabled the researcher to garner a holistic understanding of the respondents' perspective (Dawson, 2012). Bryman describes this method as one which allows the participants to discuss the subject freely, focusing on what they consider to be pertinent (Bryman, 2001). Moreover, Dawson highlights the minimal directional influence exerted by the researcher through this data collection tool (Dawson, 2012). Unstructured interviews are favoured as an exploratory research tool in healthcare. This typology was therefore chosen in the first phase of the study since it allows respondents to be more open towards providing information. The data generated through this method allows the researcher to obtain a more in-depth perspective from the participants (Low, 2007).

### 2.3.1 Questionnaire to Pharmacists

A questionnaire to pharmacists (Appendix 2) was developed to elicit their perception of ATM. The respondents were selected using non-probability purposive sampling. The criterion for respondent selection was that they had more than eight years of experience practising in community pharmacies enrolled in the National Health System (i.e. the Pharmacy Of Your Choice scheme). Prospective participants were contacted at these pharmacies and asked if they were willing to take the questionnaire. The response rate was 86% (N=86), well exceeding the recommended sample size limit of 10%.

The questionnaire incorporated both close-ended and open-ended questions. The close-ended questions were categorical 'yes' or 'no' questions, but participants were encouraged to also

express their opinions based on their experience in this area. The questionnaire gave the option for respondents to make any additional comments. It was judged that this combination of closed and open-ended questions enabled quantifiable results (Fink, 2009), but also captured a wider data set. It minimised the potential for bias arising from restricted responses linked to close-ended questions (Keeney et al., 2001).

Once formulated the questionnaire was piloted by three community pharmacists, who were requested to test it for wording and structure, with the aim of avoiding ambiguity by ensuring that the questions were clear, concise and straightforward. They were also asked whether the questionnaire covered the topic effectively and comprehensively, and to flag any questions deemed unnecessary. The questionnaire was then refined by altering the construction of two questions for clarity (Q7 and Q10).

The researcher was present during the completion of all questionnaires. This enabled consistency in the understanding of each question and also allowed for respondents to be provided with uniform definitions of relevant terms. Participants were initially asked to give their interpretation of the terminology Access to Medicines (Question 1). They were also asked for their views on whether the range of medicinal products available on the National Health Service fulfilled the criterion of access (Question 3). Other questions sought their opinion on whether the reimbursement system supported appropriate ATM (Question 2), their experience with prescriptions originating from other EU countries (Question 6) and the obstacles they encountered related to Access (Question 4). Information on mechanisms or procedures they resorted to when faced with problems of this nature was also requested (Questions 5 and 7), as were further comments (Question 8).

### 2.3.2 Unstructured Interview to Medical Doctors and Nurses

An unstructured interview was used as a primary data collection tool with the aim of exploring the perspective, experiences and attitudes of medical practitioners and nurses regarding ATM: co-stakeholders in handling access issues in a healthcare setting. As professionals, they are both in direct contact with patients encountering difficulties in ATM. The results were used as a basis to inform the guides for the semi-structured interviews. For these reasons, differentiating between the results to examine whether doctors and nurses experience differing difficulties was beyond the remit of this study.

The sample group was selected using purposive sampling which is a commonly used technique in qualitative interviewing (Dawson, 2012). The aim of these interviews was to gain insight into ATM issues encountered by key personnel with experience in this field. The respondents chosen, therefore, were actively engaged in direct patient care, in both primary and secondary settings, and had more than eight years of practice in this area. A mix of medical doctors (n=14) and nurses (n=9) enabled integration of both points of view. The sample size (N=23) was based on guidance provided by Hagaman and Wutich (2016) who estimated that common themes are identified with 16 or fewer interviews (Hagaman and Wutich, 2017). Crouch and McKenzie (2006) are in general agreement, recommending a sample size of approximately 20 for enhanced in-depth inquiry in qualitative research (Crouch and McKenzie, 2006).

All the interviews were conducted by the researcher who introduced the topic and explained the context of the research. Together with the Invitation Letter (Appendix 1B), the researcher

provided an Opening Statement to the Interview (Appendix 3) to participants and permitted them to review it in their own time, with clarifications addressed as necessary.

Participants were then asked to discuss their views on the topic and to indicate the difficulties and barriers correlating to Access that they experienced in their practice. The interviewees were able to respond freely, however, the researcher followed up on certain points which required clarification or amplification in order to ensure that these were being interpreted appropriately.

## 2.4 Phase 2

The second phase of the study targets **Objective 1A** and **Objective 1B**:

*Objective 1A: To investigate the stakeholders' perceptions of barriers in this area.*

*Objective 1B: To examine and assess how policy may impact on access and sustainability including market failures.*

The research tools used in this phase included:

- A structured questionnaire to prescribers.

This continued to build on the findings from phase 1 by exploring facets of ATM confronting prescribers and bolstering data related to Objective 1A.

- Semi-structured, open-ended interviews to policy-makers and experts in the field, targeting Objective 1B.

Schultze and Avital (2011) describe the semi-structured interview as an appropriate tool utilised widely in qualitative research. As in this study, the interview schedule generally comprises a series of pre-defined open-ended questions, which enable participants to freely voice personal opinions and debate pertinent issues. However, it is acceptable to depart from the questions outlined in the schedule (Bryman, 2001), since this research tool allows for the inclusion of additional follow-up questions resultant from the discussion (DiCicco-Bloom and Crabtree, 2006). Semi-structured interviewing is considered a flexible and effective tool for the collation of qualitative data, well-suited to health services research settings, and a frequently used data generator of stakeholder perceptions in this field (DeJonckheere and Vaughn, 2019). For these reasons, semi-structured interviews were adopted as the main research method, appropriate to consolidate and refine the data generated through this study.

### 2.4.1 Prescribers' Study: A Questionnaire

Preliminary analysis of the results obtained at Phase 1 immediately highlighted education, information and rational prescribing as meriting further investigation. A self-completion questionnaire was designed to investigate rational prescribing in relation to ATM and to develop an understanding of the prescribers' perspective.

The questionnaire was intended to obtain both quantitative and qualitative data. The first ten questions were close-ended: these are easier and quicker to answer, avoiding respondent

fatigue and encouraging higher response rate (Donyai, 2015). The final question (Question 11) was open-ended: it requested respondents to comment freely in order to collect additional data which close-ended questions preclude. The questionnaire was designed to investigate:

- The information, educational material and training that participants had received over the last twelve months relating to: medicines' use; rational prescribing; drug utilisation studies; and therapeutic guidelines (Questions 1-6 and 10); and
- Prescribers' perception of the extent of their involvement in the entry process of medicines onto the NHS (Questions 7-9).

The questionnaire was piloted by three doctors: one consultant; one general practitioner; and one speciality trainee. The same process as described at Section 2.3.1 was adopted. In this case the established criterion necessitated that the selected participants work at main general teaching hospital (Mater Dei Hospital). The schedule was adjusted in accordance with the feedback received. The main amendment comprised inclusion of the definition of rational prescribing and how the concept relates to ATM. The aim of this modification was standardisation of responses. Other changes related to clarification, structure and brevity. The final version of the Questionnaire to Prescribers is attached at Appendix 4.

The self-completion questionnaire was distributed to prescribers who had more than five years of experience. The response rate was 75% (N=187) ), well exceeding the recommended sample size limit of 10%. The cohort was selected using non-probability convenience sampling based on their availability and willingness to participate. The questionnaire was distributed in person at the various departments of the main general teaching hospital (Mater Dei Hospital). It incorporated medical practitioners engaged in hospital practice, community

practice or both. It included consultants (n=14), general practitioners (n=75) and specialty trainees (n=98).

### 2.4.2 Semi-Structured Interviews

For the purpose of Phase 2 of this research, one-to-one, semi-structured, open-ended interviews were designed for experts with this scope of obtaining data relating to specific elements of ATM. The interviews were designed to obtain a qualified understanding of the subjective aspects of the decision-making process, the problems and hindrances encountered, the differences and commonalities between the Member States and other factors which impact on ATM. Three semi-structured interviews were devised to explore different dimensions as follows:

- Component 1: Health care provision perspective (Appendix 5) N=7
- Component 2: Payer advocacy perspective (Appendix 6) N=8
- Component 3: Health economics and financial perspective (Appendix 7) N=7

For each semi-structured interview, an interview schedule was prepared incorporating a comprehensive list of points in the form of a question, which correlated to a particular facet of access. Whilst every interviewee was given complete leeway to express their opinion, the semi-structure guide ensured that the main issues were all raised with each expert, allowing recognition of predominant themes and comparability of responses. The interviews were all carried out by the researcher.

The main themes raised in the three semi-structured interview schedule are presented at Table 2.1. Whilst the context of the narrative was consistent for all three interview schedules (that of ATM and correlated issues), the perspectives being explored differed substantially. The guide for each semi-structured interview was, therefore, tailored to be in keeping with each corresponding perspective.

| Themes | Semi-Structure Interviews | | |
|---|---|---|---|
| | Health care Provision | Payer Advocacy | Health Economics |
| ATM Barriers | X | X | X |
| Positive List Entry | X | X | |
| HTA Procedures | X | X | |
| Pricing/Costs | X | X | X |
| Use of Indicators | X | X | |
| Regulatory Impact | X | X | |
| Policy Impact | X | X | X |
| Information Sharing | X | | |
| Member State Issues | X | X | X |
| EU Harmonisation | X | X | |
| Rational Use | X | | X |
| Needs Assessments | X | X | |
| Conclusions/Suggestions | X | X | X |

*Table 2.1: Main themes explored through semi-structured interviews in Phase 2*

Validation was carried out by testing the semi-structured interview schedules using cognitive interviewing.

The Cognitive Interviewing technique is based on a four-parameter model, as described by Willis (2005) and Fowler and Cosenza (2008). Cognitive Interviewing is particularly synergistic with qualitative research (Waddington and Bull, 2007). It has been found to be a valid and robust technique to test content validation of the tool being assessed (Beatty and Willis, 2007).

The validation panel was composed of three pharmacists with backgrounds in pharmaceutical policy and regulation, and the managed entry of medicinal products. Panel members were taken through the questions in each interview schedule by the researcher to test for clarity, ease of comprehension and relevance. Each question was screened and flagged for retention, omission, or revision. In addition, ancillary considerations were raised for inclusion: in this regard, the exercise also ensured that each interview schedule assimilated as comprehensive a list of key points as possible. The three members completed two rounds of validity testing for each interview schedule, which were subsequently altered to reflect the panel's comments. Alterations mainly focused on clarity and brevity.

A two-round Delphi Technique was selected as an appropriate methodology to conduct the interviews because of its value in a multi-method research technique. It is particularly suited to data collection from experts regarding specific issues (Petry et al., 2007; Sermeus et al., 2009; Elliott et al., 2011; Soon et al., 2012; Créange and Careyron, 2013). The main goal was to iteratively reach consensus amongst the group of stakeholders. Once the first round of interviews was held, the findings were collated, summarised and presented to the participants to obtain their reaction (Boulkedid et al., 2011; McMillan et al., 2016). Participants did not meet each other and each subject's responses remain anonymous, eliminating inter-

individual influences such as may occur in group interviews (Hasson et al., 2000; Steurer, 2011). Cut-off criteria preventing matters from transferring to the second round included:

- Isolated remarks which did not fit in with the overall perspective of the interview;
- Comments related to administrative system interactions of processes;
- Bureaucratic procedures;
- Matters which referenced a specific context.

During the second round of consultation, there was general agreement with the findings and consensus was reached. Some participants amplified on the text, or proposed refinements to it. Respondents also provided further details on their reasoning or used examples to illustrate a point.

The Delphi group included experts representing a range of proficiencies and backgrounds (executive and/or academic) in the fields of:

- HTA (n=3)
- Health/Pharmaceutical policy (n=3)
- Financial Provision for medicines on the National Health System (n=2)
- Pharmacoeconomics (n=1)
- Public Health (n=1)
- Medicines utilisation (n=2)
- Pharmaceutical administration and purchasing (n=2)
- Pharmaceutical regulation (n=1)
- EU fora (n=2)

A balanced representation, rather than the number of representatives, is considered to be the more important aspect of qualitative research (Linstone and Turoff, 2002).

## 2.5 Phase 3

The third phase of the study targets **Objective 1A** and **Objective 1C**:

*Objective 1A: To investigate the stakeholders' perceptions of barriers in this area.*

*Objective 1C: To determine how the European legislative infrastructure influences equitable access to medicinal products.*

### 2.5.1 Semi-Structured Interviews

During Phase 3, a one-to-one semi-structured, open-ended interview was designed to explore the pharmaceutical regulatory dimension, its interaction with policy and health care, and its impact on ATM (Appendix 8). The results generated through the research conducted during Phase 2 were also used to inform the interview schedule, enabling integration of a broader spectrum of parameters as presented in Table 2.2.

| |
|---|
| - Participants' understanding of policy and how it may influence ATM<br>- Factors which may impact the rational use of medicines<br>- Participants' perception of ATM and the problems and barriers linked to access<br>- Information and education in relation to ATM<br>- Regulatory overlap with HTA<br>- How EU legislation impacts ATM<br>- How pan-European initiatives and systems function to affect ATM<br>- Interaction between the pharmaceutical infrastructure in the EU and the health care systems of the member states. |

*Table 2.2: Main themes examined through the interview schedule in Phase 3*

The cognitive interviewing technique was once again used to validate the semi-structured interview schedule. This was carried out in accordance with the methodology used during Phase 2, as described in Section 2.4.2. The validation panel was composed of three members with experience in EU fora and pharmaceutical regulation.

The Delphi Method was once again used to conduct two rounds of one-to-one interviews. The Delphi group was composed of experts with experience in:

- EU fora (n=2)
- Pharmaceutical regulation (n=3)
- Pharmaceutical policy (n=2)

Consensus was reached following the second round of interviews. Moreover, one-to-one focused in-depth interviews were adopted to follow-up on specific issues which had been

raised during the two-round Delphi Method. These were held with those experts (n=4) who could recount personal working experiences regarding specific case studies or elucidate significant issues in greater detail. All the experts had previously formed part of the Delphi group.

## 2.6 Phase 4

The results of Phases 1-3, and more particularly the ATM supporting framework developed as part of this study, were presented to a focus group in order to achieve Research Aim 2 and Objectives 2A and 2B.

### 2.6.1 The Focus Group

Focus groups have been endorsed as a valuable qualitative research tool in pharmacy practice and an important methodology in needs assessment in the health care sector (Greenbaum, 1998; Kaae and Traulsen, 2015). This data collection technique has the potential to stimulate interactive and synergistic discussion (Leung and Savithiri, 2009), and is an appropriate means of validating results (Carey and Asbury, 2012). It is frequently used to obtain an outcome of consensus in expert groups in health research studies (Green, 2007).

Consequently, the focus group technique was deemed to be the most appropriate tool to be adopted for the final stage of this research. Its scope was to enable debate, thus challenging the respondents and spurring them to scrutinise the proposals being put forward. This, consequently, strengthened the quality of the data generated. The focus group was also used to evaluate the ATM indicators resulting from the study, which had been formulated into a Framework.

The focus group comprised experts (N=5) in the following fields:

- Pharmaceutical policy, HTA, managed entry of medicinal products;
- Pharmaceutical policy, national formulary management, medicines' supply and utilisation;
- Pharmaceutical regulation, pre-licensing assessment of medicinal products;
- Public health and pharmaceutical policy; pharmaceutical regulation, managed entry of medicinal products; and
- Pharmaceutical industry, medicines' shortages.

The members of the group were identified on the basis of their broad expertise in the area of ATM. All were well-experienced and heavily involved in participation in EU fora. Their opinion were, therefore, of great value to this research. When respondents are well-acquainted with the area under study, Morgan (1998) advocates for smaller groups. The researcher moderated the discussion, supported by an assistant moderator.

### 2.6.2 Objectives of the Focus Group

The outcomes expected from the focus group were to:

- Give their interpretation of, and provide feedback on, the study findings
- Elaborate on the application and the practical implications of the proposed Framework
- Identify issues such as weaknesses and limitations of the Framework

### 2.6.3 Focus Group Discussion Guide

As advocated by Krueger (1998), a focus group discussion guide (Appendix 9C) was used to direct the session and keep the participants on task. The guide targeted the objectives of the focus group and was designed to prompt and provide structure to the discussion, and to maximise the input of the individual participants. It was informed by the results of the study, which were used to formulate the guide.

### 2.6.4 Validation of Adopted Methodology

Since the focus group members were specifically chosen because of their high-level knowledge base, it was not possible to simulate piloting in a representative group setting. As an alternative, the methodology and questions to be asked were evaluated by two professionals with a generic comprehension of the topics under discussion, in order to vet their clarity and design. No modifications were deemed necessary.

The focus group was used to create dialogue regarding the issues, domains and indicators identified, with the scope of deriving and endorsing recommendations. It also acted as a tool to test and validate the proposals resulting from this research

### 2.6.5 Conducting the Focus Group

A letter was sent to the chosen experts, inviting them to participate in the focus group and, if they agreed to do so, requesting them to sign an attached Consent Form. The letter incorporated an Information Sheet outlining the research and summarising the context of ATM (Appendix 9A). This was followed up by a background document which briefly described the Access Framework being proposed (Appendix 9B). Participants were requested to read through the document provided and return the signed Consent Form. They were also invited to reflect on the dimensions and associated indicators which interfaced to form the Access Framework resulting from this study.

A brief introduction outlining the research context and findings was presented to the group at the start of the meeting. Using the Background Document (Appendix 9B) provided, the researcher briefed the participants on the results of the study, the framework of measures facilitating ATM determined through these findings and the principles underpinning its operation. A Discussion Guide (Appendix 9C), which introduced the postulated context and application of the Access Framework, was then used by the focus group to consider and debate different aspects of the Framework.

Definitive areas and topics emanating from the study findings and proposals, were then discussed by the Focus Group in an environment where the respondents' interactions and deliberations could be monitored and documented. The discussion lasted for three hours.

The participants were requested to consider the indicators formulating the Framework, propose any modifications necessary and validate this methodology. They were also encouraged to reflect on the practical application of the Access Framework, as well as resultant operational interactions between the Member States and at EU level. Towards the end of the debate, each participant was asked to record:

- Three points related to the practical application and implications of the Framework.
- A strength, opportunity, threat and weakness related to the validated Framework.
- Test cases of therapeutic groups proposed to pilot the Framework.

## 2.7 Data Analysis

Both quantitative and qualitative data was generated from the interviews and questionnaires. The techniques used to analyse and interpret meaning from the data content are described in this section.

### 2.7.1 Quantitative Data Analysis

Quantitative Data Analysis refers to the numerical assessment of data using a mathematical approach (Walliman, 2017). This methodology was used to study the responses obtained from the questionnaires.

In order to generate a comprehensive evaluation, the results from each question were firstly assessed individually, and then collectively. Numerical comparisons were executed manually, enabling an understanding of the different issues involved. Although the questionnaire findings were predominantly analysed quantitatively, this was combined with a component of qualitative content analysis, as described in Section 2.7.2.

### 2.7.2 Qualitative Data Analysis

Content Analysis was adopted to examine the multi-faceted qualitative data produced by this study. Walliman describes qualitative data as that derived from individuals or groups of people as a focal point of research (Walliman, 2017). It may also be applied to diverse documents (Scott, 1990).

Content Analysis consists of a replicable and systematic assignment of data into prescribed classifications (Bryman, 2001; Dawson, 2012). Assarroudi et al. advocate it as a rigorous transparent and reliable tool, allowing the derivation of practical conclusions (Assarroudi et al., 2018).

For the purposes of this study, the approach adopted was that of Directed Content Analysis, with the researcher developing the initial coding guide through the literature review. As the analysis evolved, the coding scheme was revised and modified to embrace the differentiated categories (Hsieh and Shannon, 2005; Assarroudi et al., 2018). Data generated through all the interviews, as well as qualitative information emanating from the questionnaires was evaluated through this technique.

This research also incorporated a strong element of thematic analysis. Themes were generated by sorting the codes into higher-level topics which captured a prominent aspect of the data by determining the concept connecting them. Three themes were identified, namely: policy, regulation and health system facilitators to ATM. The emergent themes were used to structure the discussion in Sections 4.2, 4.3 and 4.4 respectively. They also informed the development of an Access Framework, bolstered throughout all phases of this research, as discussed in the following section.

### 2.7.3 Development of Framework through Data Analysis

Through the analysis of data generated during Phases 1, 2, and 3, indicators were identified which facilitated ATM. These indicators were then classified into domains or stages of implementation, thus developing a supporting framework.

### 2.7.4 Analysis of the Focus Group Results

The results from Questions 1, 2 and 5 of the Discussion Guide (Appendix 9: The Focus Group) were coded and categorised under the themes established earlier in the study. The results from Question 3 were used to build a SWOT analysis of the Access Framework with the objective of optimising its strengths and opportunities whilst minimising the inherent threats and weaknesses. The therapies proposed by the participants to test the Access Framework (Question 4) were tabulated for the purpose of selecting an appropriate group with which to challenge the Framework. The emergent data was used to bolster the findings of this research, to consolidate and validate the Access Framework and to refine and elaborate on its functional and operational elements.

## 2.8 Concluding Remarks

The research design adopted for this study is outlined in this chapter. It is intented to address the aims and objectives of this research, utilising accredited literature and stakeholders knowledgeable in this area. The phases of research progression are explained, as are the quantitative and qualitative data collation mechanisms which combined to form this systematic mixed methodology. The techniques adopted for validation of the research tools, and analysis of the data are also described.

# Chapter 3: Results

## 3.1 Pharmacists' Questionnaire

### 3.1.1 Demographics

The cohort for this questionnaire comprised 86 pharmacists all having more than 8 years of experience in community pharmacy practice in Malta. Of these, 38 (44%) were younger than 45 years of age. Whilst 60 (71%) of the participants only practised in community pharmacy, the remainder also worked in the hospital (n=12 / 14%), purchasing (n=5 / 9%) or regulatory (n=9 / 6%) sectors. The male to female ratio was of the order of 1:2.

### 3.1.2 An Understanding of Access to Medicines

On being asked for their understanding of Access to Medicines, none of the respondents correlated ATM with Access to Information, whilst only 10 (12%) identified this concept with all three key elements: Availability, Affordability; and The Notion of Rational Use.

A notable group of respondents (n=33 / 38%) equated ATM with both Availability and Affordability, while 16 (19%) linked Access to both Availability and a facet of Rational Use. Access and Availability were regarded as synonymous by 23 (27%) respondents whilst 4 (5%) were unclear about the term.

Having provided their understanding of ATM, respondents were given a standardised description of this term (Appendix 1B). The majority followed this up with a discussion on

the topic with 66 (77%) of the participants expressing an interest in receiving further information and learning more about this area, and 46 (53%) remarking that it would be of direct benefit to their practice.

The results indicate that pharmacists are keen to be better informed about this subject and its implications. Recommendations put forward as an outcome of this research will build on this finding with the scope of improving the awareness and knowledge base of stakeholders.

### 3.1.3 Efficiency of the Reimbursement System in Ensuring ATM

A large group of respondents (40 respondents / 47%) were of the opinion that the Maltese reimbursement structure did not perform efficiently in relation to ATM, with a perception that the available resources could be utilised more effectively. Of the remainder: 28 (32%) felt that ATM was supported by the Reimbursement System noting, however, that there was potential for improvement; and 18 (21%) could not comment.

A problem almost universally highlighted was that of inherent wastage in the system, as presented in Table 3.1.

| Causes of Medicines' Wastage in the NHS as Reported by Community Pharmacists | |
|---|---|
| Causes | Number of pharmacists |
| Patients' sense of entitlement | 47 |
| A fear of losing that entitlement | 12 |
| Stockpiling against potential shortages | 34 |
| Pharmacists' uncertainty in establishing wastage | 21 |
| Pharmacists' lack of time to intervene diplomatically | 58 |

*Table 3.1: Causes of medicines' wastage as perceived by community pharmacists*

The respondents cited one or more factors instigating patients to claim medicines which are fully reimbursed regardless of whether they actually need them or will use them. Pharmacists' lack of time to counsel patients against wastage was noted by the greater majority of respondents (n=58 / 67%). This result is of concern and merits further investigation since counselling against wastage is linked to the promotion of rational use. Co-payment was suggested as a possible solution (n=37 / 43%), although this might affect ATM adversely.

### 3.1.4 Access and the Range of Medicines Available on the National Health System

This research sought to obtain pharmacists' perception of whether the range of medicines on the National Health System (NHS) fulfilled appropriate ATM. There was an overall acknowledgement (n=70 / 81%) that this criterion was attained, however, the potential for improvements was also identified. Notwithstanding this, an overwhelming number of respondents (n=64 / 74%) noted that innovative medicines were not made available on the

NHS due, in their opinion, to cost. This view is in direct contrast to the first statement, and suggests that the system requires review. It is, however, supported by the participants' understanding of the need to equilibrate costs with the ever-increasing pressure to introduce new therapies.

There was also a sentiment of inequities in the system. Participants (n=68 / 79%) were concerned that, whilst the majority of medicines for chronic disorders are fully reimbursed, a number remain on the negative list. They questioned the system used to determine which medicinal products entered onto the positive list, and highlighted a clear lack of understanding in this regard.

There was a perception by respondents (n=68 / 79%) that cost was the biggest hurdle preventing medicines' entry onto the NHS. Almost a quarter of participants (n=19 / 22%) suggested a review of the system with the scope of improvements targeting cost-efficiency.

### 3.1.5 Barriers to Access to Medicines

Respondents showed no hesitation in citing a number of factors which, in their experience, acted as barriers to ATM. These are listed in Table 3.2:

| Barriers to ATM as Experienced by Community Pharmacists | |
|---|---|
| Barriers to ATM | Number of pharmacists |
| Price | 32 |
| Interruptions in supply / International shortages | 31 |
| Small market size unattractive to the pharma industry | 29 |
| Regulatory issues | 24 |
| Non-entry onto the positive list / NHS | 21 |
| Lack of sufficient demand resulting in market withdrawal | 14 |

*Table 3.2: Barriers to ATM as perceived by community pharmacists*

Respondents observed that the frequency of occurrence of these problems is rising, and that the situation is becoming more complex. Shortages occur more frequently, sometimes with an abrupt cessation in supply, leaving patients in a quandary. Another reason cited for unavailability was that products are not registered due to an unattractive market compared to those of larger countries. Regulatory costs, including those associated with serialisation related to the Falsified Medicines Directive (FMD), were also raised as precluding certain products with a low turn-over and profitability from remaining on the market.

The majority of the cohort (78%) expressed concern that medicines' unavailability predisposed towards an increasing use of internet pharmacies, particularly when the same product was found to be less expensive through online purchase.

### 3.1.6 Policy, Guidelines and Access to Medicine

Analysis of the responses to this particular question indicated that differences in work experience led to notably differing attitudes and feedback from the pharmacists. In order to better evaluate the data generated, the results are presented in groups as follows:

- Group A (n=60 / 70%): those with a background in community pharmacy practice only; and
- Group B (n=26 / 30%): those with both community pharmacy as well as hospital or regulatory experience.

In the case of Group A, none of the respondents were aware of national therapeutic guidelines relevant to the use of medicines. The Out-patient Formulary List and ancillary information therein, including protocols, were referred to by 12 (14%) of the respondents who noted, however, that they did not habitually use it.

Of the respondents in Group B, 18 (21%) were familiar with some therapeutic guidelines for medicines' use in hospital. A majority (n=21 / 24%) were also aware of a Pharmaceutical Affairs platform, which included a hospital list as well as an Out-patient Formulary List, incorporating protocols associated with some of the medicines on both lists. Additionally, they were familiar with entitlement parameters which were available on the same platform. The Medicines Authority website was cited by 12 (14%) respondents as a reference indicating which medicinal products should be available on the market.

The marked difference in the responses between the 2 groups implies that outreach of pertinent information to community pharmacists is insufficient. All the respondents in Group A (n=55 / 64%) and a majority (n=20 / 23%) of respondents in Group B preferred contacting a central department to obtain information regarding entitlement issues, prescriber restrictions or non-availability problems. Some respondents (n=9 / 10%) alluded to guidance given regarding the use of alternative products in cases of positive list shortages but remarked that this was not always forthcoming.

All respondents stated that wholesale dealers and medical representatives were a primary source of information about medicines, with 55 (64%) also citing the Medicines Authority website and 62 (72%) citing the British National Formulary. None of the respondents had Standard Operating Procedures which outlined how to address issues regarding ATM. Again, none of the respondents could reference a pharmaceutical policy in relation to medicines' use. Neither did they associate the use of policy as a means of overcoming barriers to access.

### 3.1.7 Dispensing to EU Nationals from Other Member States

A notable number of respondents (n=35 / 41%) had experienced at least one occasion when they had been unable to supply a European Union (EU) citizen from another Member State with their medication. The most common examples mentioned were diuretics, anti-inflammatories cardiovascular preparations and anti-depressants.

When faced with such problems, 63 (73%) participants used the British National Formulary as their primary source of reference in identifying the product, whilst 40 (47%) also resorted to the Medicines Authority website to investigate whether the product was on the market. In this context, respondents noted that including the names of the wholesaler distributing the product would make this user-friendly platform more complete. None of the respondents had adopted a Standard Operating Procedure to address this issue.

## 3.2 Unstructured Interviews to Medical Practitioners and Nurses

Unstructured interviews (N=23) were undertaken to obtain insight into the perceptions and experiences of medical practitioners (n=14 / 61%) and nurses (n=9 / 39%) in relation to ATM.

Content analysis of the interviews identified the following themes:

- Medicines entry into the NHS;
- Physical availability of medicines;
- Equity in the reimbursement system; and
- Information and education.

### 3.2.1 Medicines Entry into the NHS

There was an almost universal perception that doctors have no control and very little influence on ATM in terms of positive list outcomes. Participants described the entry process onto the formulary as a “constant battle”.

In particular, innovative therapies were noted to be introduced very slowly, preventing a number of patients from receiving gold standard treatment. It was emphasised that, since the patient pool willing and able to purchase these therapies out-of-pocket would be very limited, innovative medicinal products are not customarily marketed. When they are, the price is typically on the high side. Targeted therapies, or biologics, were cited as examples of this situation. Another group of preparations mentioned were those whose added value lay in their potential to reduce the use or cost of resources, such as hospital stay, outpatient monitoring, number of investigations and surgical interventions.

Of the 14 hospital doctors interviewed, almost half (n=6 / 43%) indicated that, having researched a product and made a robust case for its entry, it was often the case that the department would receive no feedback or rationale as to why this was not accepted. Neither did there seem to be transparent parameters on which the entry process was structured. This backdrop discouraged initiatives to propose new medicinal products onto the formulary.

Almost all the participants (n=21 / 91%) noted that it is sometimes possible to circumvent the system by obtaining medicines on a named-patient basis: however, this is a pedantic and time-consuming solution, albeit one habitually resorted to.

It was also highlighted that patient demographics are changing and that the dynamics of the entry system onto the positive list does not accommodate this. Doctors observed that they were now confronted with diseases and disorders which were not ordinarily encountered previously, and that the range of medicinal products on the NHS does not cater for this.

### 3.2.2 Physical Availability of Medicines

There was consensus amongst participants that once a medicinal product had been authorised for entry onto the NHS, the next obstacle was usually its supply. The standard timelines for the product to actually become available to patients was stated to typically exceed 12-15 months. In the intervening time, patients are treated with the therapy available on the formulary. Switching over patients once the new product becomes available disrupts the utilisation trend established for the old, potentially leading to expired stocks. It is also not unusual for the new product's reserves to run out much earlier than estimated as a result of the difficulty in forecasting patient numbers across relatively long timelines.

Medicine shortages was a related issue which emerged very clearly, with both doctors and nurses of the opinion that this problem occurred systematically and with insufficient warning. It impacted both patient care and workload, since patients generally returned requesting an alternative product. It was highlighted that, in this case, substitution from the range of medicines on the positive list may only be possible with more expensive or less effective products.

Information surrounding the problem was generally inadequate, including the estimated time to resolution. Patients routinely omitted doses hoping that the stock-out was temporary.

### 3.2.3 Equity in the Reimbursement System

Doctors perceived there to be a level of discrimination in the way the reimbursement system operates. Although the intention is for medications related to chronic conditions to be fully reimbursed, there are a significant number of chronic disorders which are not incorporated into the scheme. This results in no reimbursement for medicinal products related to certain conditions. Medical practitioners found it difficult to explain the situation to the patients concerned since there seemed to be no rationale underlying the situation.

The way in which the named-patient system operates was also considered to be discriminatory since the product is not approved generically for all who may need it, but rather on an individual basis for those patients whose consultant made a request.

### 3.2.4 Information and Education

Through their work experience, both doctors and nurses reiterated that there was a low level of public awareness about medicines and their use. Participants emphasised the importance of education and information as an integral factor in improving ATM with the aim of empowering patients to take a more active role in their own health care: understanding and monitoring their response to the prescribed therapy, being compliant, not over-stocking and complementing medicines' use with lifestyle changes which prognosticated for better clinical outcomes.

Participants perceived there to be an over-emphasis on medicines' use, which should be equilibrated by increased education in this area. This approach would support the rational use of medicines and constitute the optimal treatment of the disorder.

Medical practitioners also pointed out that they depended largely on medical representatives for information: both about new medicinal products, as well as for feedback for products in use.

## 3.3 Prescribers' Study

Thematic analysis of the results derived from Phase 1 of this study highlighted an area which merited further investigation: that of rational prescribing, which is an integral component of ATM. This section describes the results of a questionnaire which investigated prescribers' (N=187) experiences in this area, and in particular the associated information, education, and feedback they receive.

### 3.3.1 Information, Educational Material and Training in Rational Prescribing

The respondents were asked how frequently they had received information or educational material related to the rational prescribing of medicines.

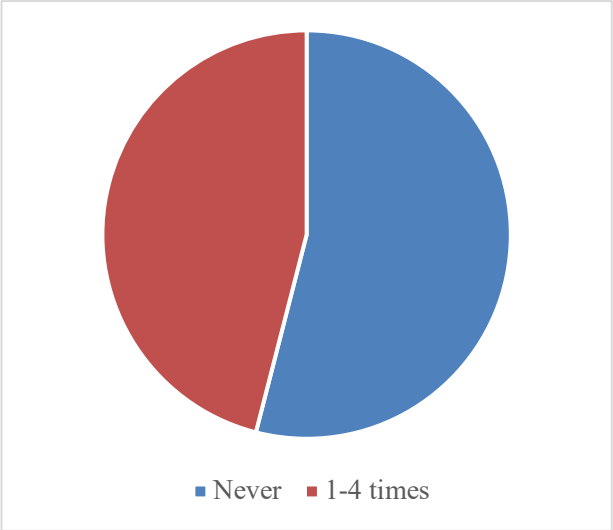


*Figure 3.1: Receipt of information / educational material regarding ATM - Frequency*

As illustrated in Figure 3.1, 45% of participants stated that they had received information or educational material regarding rational prescribing between one to four times over the last twelve months, with none having received any such literature more than four times a year. The majority (55%) claimed to never have received this type of documentation during this period.

Participants were questioned about the number of training sessions available to them addressing medicine's use. As depicted in Figure 3.2, 27% of respondents stated that they had attended between one to four such sessions over the last twelve months. However, they noted that these were company sponsored events.

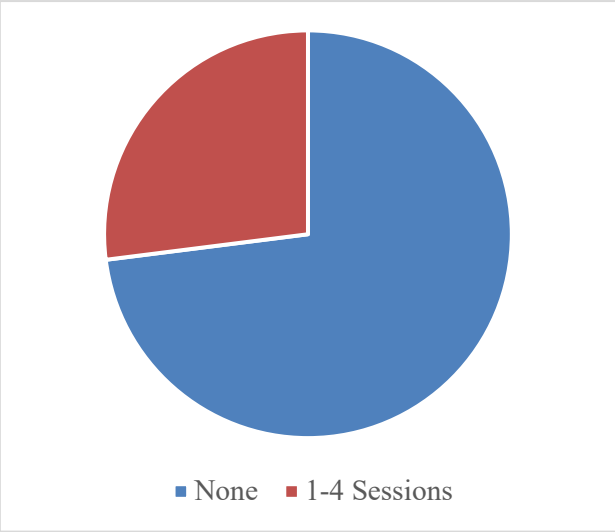


*Figure 3.2: Availability of Training Sessions regarding ATM for Prescribers*

### 3.3.2 Therapy Guidelines, Protocols and Drug Utilisation Evaluations

When asked whether standardised therapeutic guidelines or protocols were readily available to them, the majority of respondents (71%) stated that they were unaware of any. A minority (6%) referred to protocols posted on a Formulary Platform. The remainder (23%) specified National Institute for Health and Care Excellence (NICE UK) guidelines.

The respondents, who were all engaged within the National Health System (NHS) were asked about their involvement in drug utilisation evaluations. None of the participants had had this experience, and nor had they received any feedback on utilisation studies or audits of medicines on the NHS.

### 3.3.3 The Choice and Entry of Medicines on the Formulary

The overwhelming majority (73%) of prescribers stated that they were not actively involved in the choice of medicines available on the formulary. Approximately 21% were aware that consultants have the opportunity to make requests to the Drugs and Therapeutics Committee, but that these are rarely acceded to.

Prescribers were asked for their views on the procedures and decision-making process used for new medicinal products to be included on the positive list. A minority of respondents (5%) had some level of awareness of the procedure used. The majority (81%) were of the opinion that the decision-making process was mainly financially driven.

Approximately 23% were aware that a request could be put forward but that no feedback was forthcoming thereafter, and the greater majority (72%) were not aware of any such procedures / processes.

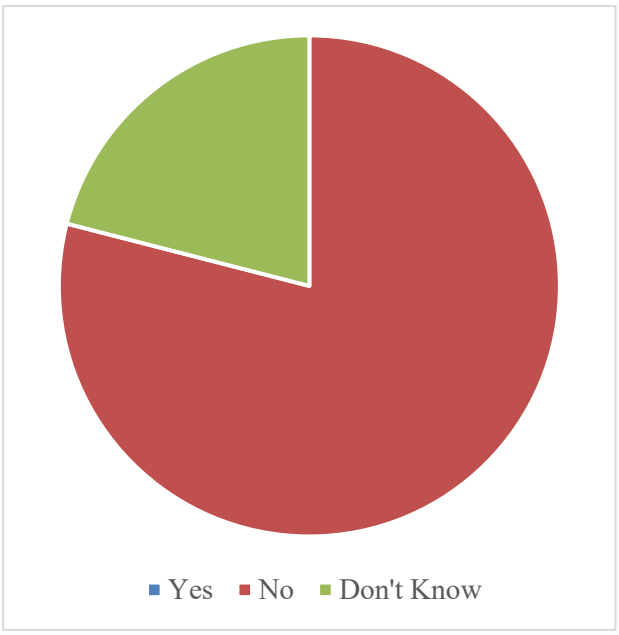


*Figure 3.3: Process of Inclusion of New Medicines in the Formulary - Effectiveness*

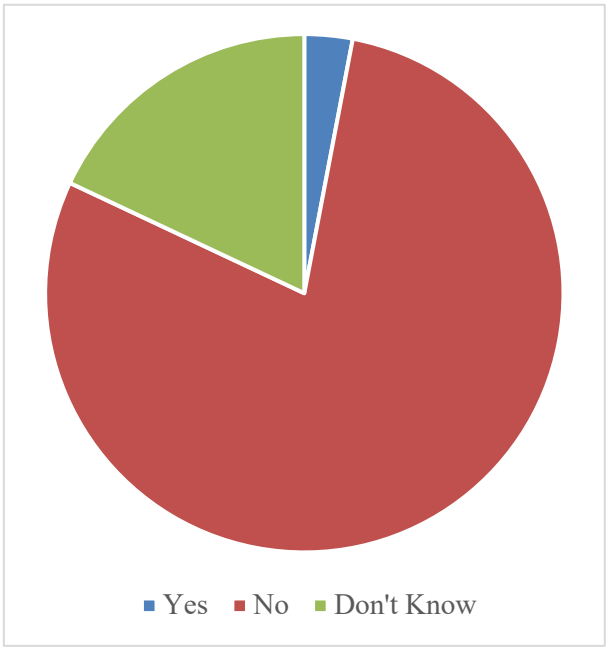


*Figure 3.4: Process of Inclusion of New Medicines in the Formulary - Feedback*

When asked for their opinion of the process of inclusion of new medicines in the formulary, the majority of respondents did not consider the system to be effective (79%) or responsive (79%): in fact, only 3% of participants received feedback following persistent requests (Figure 3.3 and Figure 3.4).

### 3.3.4 Changes to the Formulary and Initiatives Targeting Prescribing Behaviour

Table 3.3 depicts the means by which prescribers become aware of amendments to the formulary. The majority (n=119 / 64%) considered the notification system to be ineffective and not user-friendly.

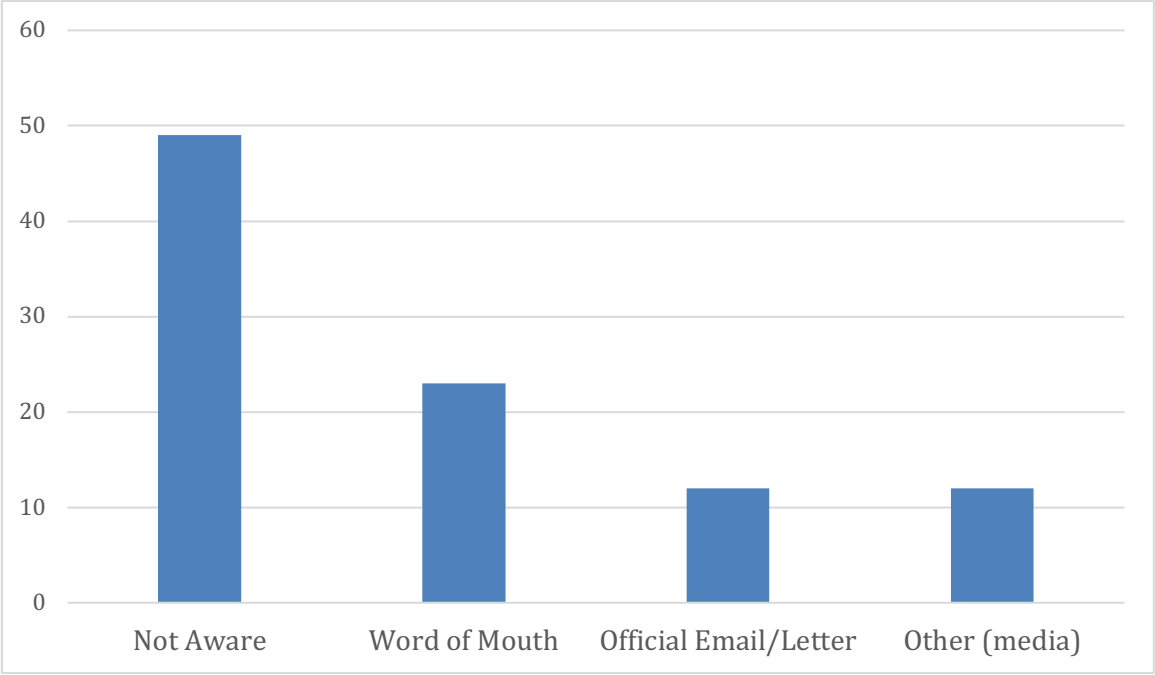


*Table 3.3: Means of Notification of Formulary Changes to Prescribers*

On the other hand, consultants were the only ones to receive detailed emails from the NHS purchasing department outlining amendments to the positive list.

Participants were questioned about their involvement in, or awareness of, prescribing modification schemes. Half of the cohort had no experience of initiatives targeting the modification of prescribing behaviour. Of the remaining 50%, 11% noted this experience as international whereas a notable 39% referred specifically to guidance addressing antibiotic use. Those participants with experience could not comment on the success of these initiatives since they had received no feedback.

### 3.3.5 Sources of Information on Medicinal Products

When asked to name their sources of information regarding medicinal products, the majority (n=147 / 79%) of participants cited medical representatives as their main source. Besides the Summary of Product Characteristics (SmPC) and journals, prescribers referred to Team Discussions and company sponsored events as other sources of information. A minority of respondents (n=16 / 9%), all of whom were consultants, stated that they also received information through the Drugs and Therapeutics Committee (DTC). The results are presented in Figure 3.5.

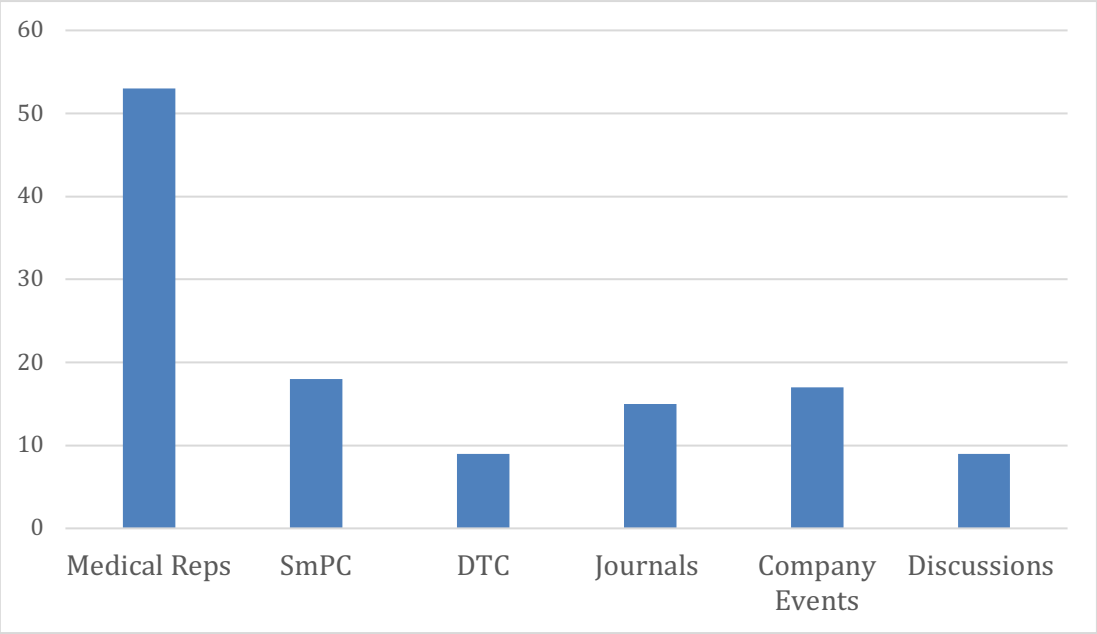


*Figure 3.5: Sources of Information on Medicines*

Additional comments were coded into the following three categories:

- More effective communication regarding rational prescribing;
- System requires a radical upgrade; and
- Pharmacists are well-placed to take more initiatives in this area.

Furthermore, respondents emphasised that financial restrictions discouraged attempts for new medicines to be placed on the formulary.

## 3.4 Semi-structured Interviews

This section presents the key issues impacting on ATM, which were identified through thematic coding of the data generated through the semi-structured interviews.

### 3.4.1 Pharmaceutical Policy

The results from the semi-structured interviews indicate that a holistic policy purposefully addressing ATM, with clear strategic parameters, would be a tool of force within this area. Participants noted that assorted policy decisions, by different protagonists, impact ATM directly or indirectly with varying consequences. There was a perception that in many instances, these decisions were taken to address specific circumstances as and when they arose, and did not necessarily form part of a long-term plan of action. It was also noted that roles and responsibilities pertaining to policy and ATM were undefined.

There was consensus amongst stakeholders that current EU policy objectives incorporated over-arching pharmaceutical elements, such as medicines pricing. However, they were not generally optimistic that these goals would be achieved in the near future.

### 3.4.2 Health Technology Assessment

The issue of Health Technology Assessment (HTA) was a recurring theme which resonated across all the perspectives explored through the semi-structured interviews.

Participants acknowledged that the differing spectrum of medicinal products available on each country's NHS was due to a significant extent to contrasting applications of HTAs. They were of the general opinion that this issue was unlikely to be resolved imminently, citing the various unsuccessful attempts spearheaded by the Commission to do so: the latest

being the concerted effort made by the German presidency over the last six months of 2020. Despite a strong commitment to the endeavour, including an offer to share the German HTAs with other Member States, the initiative to bridge differences between territories was unsuccessful.

The experts emphasised that HTAs are an essentially scientific tool. However, it was noted that there exists a level of subjectivity resultant from the assessor's referencing and interpretation of the documentation when evaluating comparative effectiveness. Moreover, through their work experience, participants concluded that assessment of the data does not flow seamlessly from the regulatory component to that of the HTA in terms of standards and norms, such as what the clinical studies should determine, and which endpoints to use. It was noted that HTAs are based on analysis and synthesis of different unrelated elements which are then compared to those of another product, and that this process differs substantially from the more clear-cut and evidenced benefit-risk assessment associated to marketing authorisations.

As long as the requisites of the evidence for HTAs remain unaligned between the Member States, the goal of joint assessment of the clinical domains of the HTA remains unattainable. It was also noted that the vast disparity between the Member States in the non-clinical domains of the HTA make a joint HTA conclusion currently impossible.

### 3.4.3 The Small States

The experience of a number of stakeholders was that the smaller Member States face particular problems associated with ATM. Participants noted that the limited patient pool generates stunted profits, making the territory less attractive to the pharmaceutical industry. In addition, it is habitually the case that only a finite (one or two) number of products from each category would be viable, discouraging newer medicines, possibly offering advantage over the old, from being introduced in the territory.

There was consensus that, since the pharmaceutical companies decide unilaterally where and whether to market their products, smaller Member States are often left struggling to obtain certain medicines. Participants reported that, inevitably, in these circumstances, governments (in the form of an executive arm) are forced to intervene to secure products for the NHS. Moreover, it was noted that the situation is exacerbated by regulatory obligations and costs which are similar to those in the larger Member States. These include the resource required for the grant of a marketing authorisation and the running costs of maintaining the product on the market throughout its lifecycle. Examples were cited, such as: the outlay due to marketing authorisation renewal; the overheads related to pharmacovigilance; the cost of variations; and the expenses associated with product serialisation.

A number of experts emphasised that, as a result of their particular context, the smaller states have very limited power to negotiate prices. As a consequence, smaller countries face fundamental problems with two key pillars of access: availability and affordability.

The Valletta Declaration Group was referred to as a forum for cooperation between a number of Member States. However, it was also noted that more progress is required.

### 3.4.4 Pricing and Reimbursement

Participants were unanimous that, much like the controversial HTAs, medicines pricing was a foremost issue in ATM. Repeated attempts to establish a single pan-European price per product have been unsuccessful. There was consensus that there exist notable variations in the prices of medicinal products between Member States. These differences were not limited to originator or branded products, but could also be seen amongst generics and parallel traded products.

A number of experts stated that pricing does not necessarily correlate to the country's Gross Domestic Product (GDP): in their experience higher priced medicines could be found in territories with a relatively lower GDP. Additionally, generic preparations may not always be present in certain markets. Participants expressed their concern that at times the generic may actually be more expensive than the originator.

There was agreement that External Price Referencing (EPR) is the formula most commonly used to ensure fair pricing. Through experience, participants noted that EPR motivated the industry to launch products in the higher-priced market first, thus establishing a benchmark for the other Member States. It was highlighted that it was not necessarily the smaller

Member States that experience delayed access, but the lower priced ones, with Luxembourg cited as an example of a small country with comparatively fast access.

Moreover, there was a general awareness that official prices do not truly reflect the actual cost. It was also suggested that once a price is set via EPR, a monitoring system flagging price revisions should be operated. Managed entry agreements were noted as a more recent pricing mechanism being utilised for new technologies. Participants were uncertain as to how effective this approach was but were in agreement that it offered a viable alternative to EPR.

The perspective of the stakeholders representing finance was unanimous and unequivocal. They adopted a capping approach advocating budgetary limits. They maintained that, as long as spending was curtailed below a given ceiling, it was up to the Health Authorities to decide on spending structures. Experts in payer advocacy agreed that all countries operate under budgetary restrictions. However, they accentuated that this must be balanced by the responsibility of ensuring rapid access to new therapies which translated into realistic health gains. They also called attention to inequities which still exist in the reimbursement system of some Member States. In addition, they raised the issue of sustainability, which should be an important parameter of the system, and which was not currently overtly addressed.

### 3.4.5 The European Union and Access to Medicines

The pharmaceutical policy adopted by the European Commission (EC) was endorsed by the participants, who noted that a major objective was to ensure access to affordable medicines

to all patients in the EU. Stakeholders highlighted a recent commitment in EU strategy to revise the pharmaceutical legislation. They emphasised that this presented an opportunity to recommend changes to improve access.

There was consensus that the current legislative framework does not provide a solution to those situations where the industry decides not to market a product in some parts of the EU. It was noted that the industry has the prerogative on what to research and develop, where and when to market, and, to some extent, on pricing and prescription-only or over-the-counter status. Experts cited cases where medicines authorised through the centralised procedure were still not placed on the market of a number of Member States, mainly the lower-priced or smaller territories. Initiatives such as marketing authorisation accelerated pathways were seen as being of little use to those countries where the product would still not be marketed. There was agreement that although the regulatory infrastructure provided a common platform throughout the EU, the way in which it affected the Member States varied. Moreover, the continuous evolution of the legislative framework (for instance, the recent Falsified Medicines Directive) tended to carry with it increased costs which would inevitable be borne by the payer, possibly resulting in decreased access.

Conversely, issues such as transparency in pricing remain unresolved. The stakeholders also called for the need for certain issues related to the Cross-Border Health Care Directive to be addressed, such as electronic prescribing and difficulties in establishing product availability as well as reimbursement price. The Transparency Directive was also flagged as meriting further attention since not all Member States are currently able to comply with the maximal

time period imposed between the grant of the marketing authorisation and the decision on reimbursement. Table 3.4 presents the benefits and drawbacks of EU Integration, derived through content analysis of the interview results.

| **Benefits/Drawbacks of EU Integration as Reported by Stakeholders** | |
|---|---|
| **Benefits** | **Drawbacks** |
| Clearly established standards and norms. | Fast-changing/demanding EU environment. |
| Monitoring, auditing and enforcement of standards and outcomes. | Increased administration and bureaucracy. |
| Increased fields of specialisation in this sector. | Increased resource demand. |
| Technical support offered by EU fora. | Small State specificities overlooked. |
| Networking and co-operation with other member states. | Impact on NHS sometimes out of proportion or counter-productive to intended patient benefit. |
| Financial support for training and capacity building. | Over-powering strength of Big Pharma lobby. |
| | Corporate interests possibly superseding those of the patient population. |
| | EU rhetoric does not necessarily result in tangible outcomes (e.g. Pricing and HTA). |

*Table 3.4: Stakeholders' Perceptions of the Benefits/Drawbacks of EU Integration*

### 3.4.6 Information, Education and Rational Use

Stakeholders noted that ATM, rational prescribing and rational use are inexorably linked. It was universally acknowledged that more concerted effort was required to bolster unbiased information collation and dissemination, and education influencing prescribing patterns and targeting optimal utilisation of medicines. Additional important information which would enable evidence-based decision-making included the collation and analysis of data such as volume trends (numbers of patients and prescriptions) and price trends (price per prescription, price per Defined Daily Dose). The need for audits to produce real evidence and correlate utilisation data with outcomes was also emphasised. There was consensus that a holistic pharmaceutical policy would address gaps in this area.

## 3.5 Developing a Structured Approach to Access to Medicines

This section presents the analysis and evaluation by the focus group of the study findings, enabling further discernment of the issues involved. The focus group was also used as a tool to test and validate the proposals emanating from the research and to consolidate the framework of measures designed to support ATM.

### 3.5.1 A facilitating framework

In line with Research Aim 2, the data generated through phases 1, 2 and 3 of this study were used to derive indicators which enabled sound decision-making strategies optimising ATM.

These indicators were clustered into domains delineating the context when they might be logically actioned, as depicted in Table 3.5.

| **Access Framework as Proposed to the Focus Group** | |
|---|---|
| **Domain** | **Indicators** |
| Uptake | • Pricing / Reimbursement<br>• Forecasted cost-effectiveness / Therapeutic Value<br>• Prospective public health gains (health strategy, data regarding prevalence)<br>• Projected budgetary impact<br>• Affordability / Sustainability |
| Utilisation | • Availability / Shortages<br>• Rational use: protocols / national treatment guidelines<br>• Rational prescribing<br>• Dispensing / Counselling<br>• Public Campaigns (educational material)<br>• Feedback from health care professionals and patients |
| Audit | • Prescribing or dispensing database incl. patient numbers<br>• Actual reimbursement and expenditure data<br>• Utilisation studies targeting evidence-based treatment outcomes |
| Re-Evaluation | • Audit results: do these correspond to the expected cost-effectiveness and public health gains?<br>• Does the medicinal product satisfy the Access Framework indicators?<br>• Should treatment guidelines and protocols be re-appraised? |

*Table 3.5: A Proposed Framework Supporting Access to Medicines*

### 3.5.2 Domains and Indicators Denoting the Access to Medicines Framework

| **Access Framework as Endorsed by the Focus Group** | |
|---|---|
| **Domain** | **Updated Indicators** |
| Uptake | • Pricing / Reimbursement<br>• Forecasted cost-effectiveness / Therapeutic Value<br>• Prospective public health gains (health strategy, data regarding prevalence)<br>• Projected budgetary impact<br>• Affordability / Sustainability<br>• *Expected clinical effectiveness, forecasted cost-effectiveness*<br>• *Prospective public health gains (therapeutic value)*<br>• *Horizon scanning followed by HTA* |
| Utilisation | • Availability / Shortages<br>• Rational use: protocols / national treatment guidelines<br>• Rational prescribing<br>• Dispensing / Counselling<br>• Public Campaigns (educational material)<br>• Feedback from health care professionals and patients<br>• *Involve patient organisations* |
| Evaluation | • Prescribing or dispensing database incl. patient numbers<br>• Actual reimbursement and expenditure data<br>• Utilisation studies targeting evidence-based treatment outcomes<br>• *Utilisation of real-world data* |
| Re-Appraisal | • Audit results: do these correspond to the expected cost-effectiveness and public health gains?<br>• Does the medicinal product satisfy the Access Framework indicators?<br>• Should treatment guidelines and protocols be re-appraised?<br>• *Audit results: do these correspond to the expected clinical effectiveness, cost-effectiveness, therapeutic value* |

*Table 3.6: Finalised Access Framework with Updated Indicators Derived from the Focus Group*

The framework proposed to support ATM (Table 3.5) was discussed by the focus group participants who were asked to consolidate and validate this tool. Whereas the domains were fully endorsed, some modifications and additions to the indicators were recommended. The finalised Access Framework is presented in Table 3.6, which includes the updated indicators in *italics*.

### 3.5.3 Application of the Access to Medicines Framework

The issues raised relating to the application of the Framework are listed in Table 3.7.

| **Factors to be Considered in the Application of the Access Framework** |
|---|
| - Financing and co-ordination modalities of the Access Framework to be effectuated by the EC.<br>- Scientifically based policies supporting ATM to be elaborated at Member State level.<br>- ATM definitions to be established/incorporated into the Medical Dictionary for Regulatory Activities.<br>- Parameters (e.g. effectiveness, therapeutic value) to be integrated into the assessment of medicinal products, including in Accelerated Pathways.<br>- EU-wide centralised HTA's to be restricted to the scientific component for subsequent adaptation at Member State level.<br>- Twinning systems and Joint Procurement programmes between Member States to be upheld by the EC.<br>- Enhanced mechanisms to enforce the marketing of medicinal products throughout the single market to be implemented.<br>- Audit strategies to be realised in the Member States and sustained in a European Forum.<br>- Domestic industry encouraged to supply the Member States' markets to improve self-sufficiency. |

*Table 3.7: Measures Related to the Application of the Access Framework*

The members of the focus group subscribed to the recommendations underlying the implementation of the Framework. It was unanimously agreed that this could only be successfully undertaken at the present time if allowed to be customised and flexibly operated by each Member State, with a gradual uptake of the indicators. The support and coordination at the level of the European Commission in connection with specific indicators was also seen as a positive way forward.

### 3.5.4 SWOT Analysis of the Access to Medicines Framework

The members of the focus group collaborated to carry out a SWOT analysis of the Access Framework. The results are illustrated at Table 3.8.

| **STRENGTHS** | **WEAKNESSES** |
|---|---|
| • Cohesion of procedures, increasingly conforming scientific standards.<br>• Inclusion of therapeutic value/effectiveness into the decision-making process.<br>• **Increased pan-European homogeneity coupled with an allowance for Member State flexibility.**<br>• **Accessibility assistance and facility to all Member States on all listed indicators.**<br>• **Co-ordinated and collaborative approach.** | • Insufficient real-world data available.<br>• Risk that the body co-ordinating the Access Framework is hijacked by the industry.<br>• Reluctance by governments to commit to policies in this sector.<br>• Regulating pathways not adequately explored.<br>• **Disparate health cultures and national legislations; language barriers.** |
| **OPPORTUNITIES** | **THREATS** |
| • Collation and comparison of data from the Member States.<br>• Increased strength of the Member States versus the industry.<br>• **Medicines with proven effectiveness prioritised.**<br>• **Data gained from audits can be used to validate effectiveness/optimise the system.**<br>• **Maximised assets where there is a lack of resources (scientific and financial) and/or skill mix.** | • Industry's strength as a lobby group.<br>• Purchasing power inadvertently undermined in some Member States; lack of competition/centralisation may put some small/micro enterprises out of business.<br>• Decision-making in the public procurement of medicines not appropriately balanced between national competent authorities, industry, and governments.<br>• **Lack of political will by Member States due to the perception that politicians will lose power.**<br>• **Backlash from the industry and/or patient groups.** |

*Table 3.8: SWOT Analysis of the Access Framework*

Comments cited by more than one expert are indicated in bold.

### 3.5.5 Test Cases for the Access to Medicines Framework.

Participants were asked to recommend medicinal products which could act as the initial candidates for the Access Framework.

| **Recommended Initial Candidates for the Access Framework** | | | |
|---|---|---|---|
| **Class** | **Medicinal Product** | **Indication** | **Approximate Cost (€)** |
| CAR T-cell Therapy | Kymriah®<br>Tisagenlecleucel | B-cell acute lymphoblastic leukemia | 458,000/course |
| | Yescarta®<br>Axicabetagene Ciloleucel | B-cell lymphoma, Follicular lymphoma | 360,000/course |
| | Tecartus®<br>Brexucabtagene Autoleucel | Mantle cell lymphoma | 360,000/course |
| Gene Therapy<br>(One-time treatment) | Luxturna®<br>Voretigene Neparvovec | Retinal dystrophy | 820,000 |
| | Zolgensma®<br>Onasemnogene Abeparvovec | Spinal muscular atrophy | 1,900,000 |
| | Zynteglo®<br>Betibeglogene Autotemcel | Beta Thalassemia | 2,700,000 |
| Tissue Engineered Therapy | Holclar®<br>Autologous Human Corneal Epithelial Cells | Limbal stem-cell deficiency | 91,000/course |
| Immunotherapy | Danyelza®<br>Naxitamab | Neuroblastoma | 965,800/year |
| | Blincyto®<br>Blinatumomab | Lymphoblastic leukemia | 676,000/year |
| Chemotherapy | Folotyn®<br>Pralatrexate | T-cell lymphoma | 772,000/year |

*Table 3.9: Recommended Initial Candidates for the Access Framework*

Table 3.9 depicts therapeutic agents which were suggested as preliminary medicines with the potential to be reviewed through the Access Framework

CAR T-cell therapeutic agents were universally acknowledged as the therapeutic group of choice for this purpose. The Focus Group participants felt that amongst the criteria which could be considered when selecting candidate therapies, these should include a conditional authorisation of the product and cost.

## 3.6 Concluding Remarks

This chapter presented the results generated through this research. The findings contextualised the obstacles discerned by various key players in the field of ATM. The perspectives of these stakeholders are important in order to develop an understanding of the shortfalls in the existing infrastructure, allowing recommendations to be made in this context. Evaluation of this data enabled a conceptual framework aiming to mitigate challenges in medicines' access to be proposed. The results may be summarised under the following headings:

A. Policy

1. Policy as a tool promoting ATM **not fully understood** or implemented
2. Difficult for a pan-European policy to accommodate the **divergent** healthcare models in the Member States
3. General consensus against further **Europeanisation** in the pharmaceutical arena

B. Regulation

1. Current regulatory framework fails to mitigate **Access** issues
2. Ongoing initiatives have brought **little tangible** overall benefit
3. Scientifically-established norms, technical support, networking and co-operation are major E.U. **advantages**

C. Facilitating an ATM Framework

1. **Uptake**: Reimbursement, Affordability, Sustainability
2. **Utilisation**: Shortages, Rational Use through Protocols, Educational Material
3. **Audit**: Utilisation Studies, Prescribing Databases, Patient Registers
4. **Re-Evaluation**: Re-Appraisal, Actioning of Audit Results

# Chapter 4: Discussion

## 4.1 Context

A framework for improving Access to Medicines (ATM) may only be developed once the current context has been benchmarked. The findings of this research shed light on the perceptions, attitudes, knowledge and awareness of major protagonists working in the field. They provide insight into the barriers hampering ATM thus allowing the possibility of identifying methodologies to overcome them.

The study highlights the fact that deterrents to ATM are entrenched, and sometimes replicated at various strata of the health system. This supports an approach which embeds drivers to Access in the wider health system domain.

The results not only support the identification of ATM enablers, but also direct where such interventions may best be introduced. This context goes beyond that of the individual Member States, each of which is responsible for defining and delivering health care within their territory. The Commission also has an established role in supporting and complementing national health policies (Article 168 of the Treaty on the functioning of the European Union) by developing facilitating frameworks. This is particularly the case when Member States face difficulty in working alone or when cross-sectoral action is appropriate. The outcomes of this study demonstrate that the multiplicity of factors influencing ATM are not only specific to the Member States but are overarching at a pan-European level. Therefore, for the challenge of ATM to be successfully mitigated, measures must be taken conjointly at both European Union (EU) level and in the Member States.

The results of this study represent a collation of insights from a broad spectrum of stakeholders interpreting how policies and legislation, as well as processes and operations influence ATM in practice. The findings are presented and discussed as domains portraying key areas for potential action. Most of these areas are already rooted in European Health Systems, but changes could be implemented to improve resiliency against current barriers and to strengthen the Member State's infrastructure to consciously target and improve ATM.

## 4.2 Policy and Access to Medicine

The study results, reinforced by the literature review, identified six Member States as having a documented medicines' policy (MMP): Greece, The Netherlands, Portugal, Slovakia, Latvia and Hungary. One possible cause for this lack of a readily sourced policy document in the greater majority of the European Union is provided by Hoebert et al. (2013) who observe that policy development and dialogue is often activated when an appropriate political window presents the opportunity, and that political pressure is commonly required for a National Medicines' Policy (NMP) to be instituted (Hoebert et al., 2013). For this to occur, policy must be understood to be a valuable tool which supports the attainment of health goals.

### 4.2.1 The Connotations of Policy

The results of this study point to a lack of understanding of what should actually constitute medicines' policy. Many of the stakeholders equated it to issues related to pricing and reimbursement, and with the need for medicines to be of an appropriate standard of safety, quality and efficacy. An overview of the national policies available illustrates that they mainly focus on concerns such as price and expenditure control, reimbursement and medicines' utilisation, with mention sometimes made of HTA. The World Health Organisation (WHO), a long-standing champion of medicines' policy, emphasises that this should document a formal commitment towards a country's aspirations, values and priorities in the pharmaceutical sphere, under-pinning clearly defined medium and long-term aims and the strategies to achieve them (Organisation, 2003). Policy, therefore, should also be structured so as to address hindrances to such goals, particularly in the case of predominant and over-arching themes such as ATM. The vast majority of stakeholders did not identify policy as a means towards achieving ATM; policy was perceived as a narrative delineating the control, regulation and delivery of services rather than a tool towards the realisation of specific aims.

The study results also showed that health care professionals were easily able to recognise diverse barriers to ATM, which they had experienced at first-hand. However, they did not regard a lack of cohesive and documented policy to be an obstacle. An interesting corollary was that stakeholders were unable to nominate a National Medicines Policy with a focus on Medicines' Access within the context of a Member State's economic, social and health priorities, despite the fact that ATM is currently prominent on the pharmaceutical agenda.

There were various interpretations of the term *policy*, ranging from sporadic decisions to entrenched notions of practice. Stakeholders clearly connected such practice norms or decisions with the potential to impact ATM directly or indirectly, sometimes as a desirable outcome but more often as an unwanted and generally negative consequence. Since medicines' accessibility may be influenced by several diverse, complex and sometimes unconnected factors, intermittent attempts to resolve issues as they arise may only serve to create further problems. The data showed that this approach of ad hoc solutions leads to fragmentation in terms of Medicines' Access, both within the National Health System (NHS), as well as between the public and private (out-of-pocket) sectors, hindering the realisation of planned and positive outcomes allied to improvements in public health.

It is clear that the advantages that a documented NMP may bring are not always sufficiently understood. This inevitably leads to a lack of oversight that further anchors the status quo. The experience of stakeholders substantiates how Medicines Access may be unintentionally undermined through not being established, defined and prioritised as a strategic goal. A transparent, cohesive and documented national policy which explicitly upholds ATM would provide clear direction and serve as a platform in fostering Access as a health priority; one rooted in principles such as timeliness, equity, transparency, cost-effectiveness and sustainability. For such a policy to be fit for purpose, it must be developed in accordance with each Member State's needs and resources, and must also be participative and inclusive of all actors involved.

### 4.2.2 The Policy Process

Besides a formal commitment to the values and aspirations of the country, a medicines policy should define medium and long-term goals, as well as the methodologies to implement and sustain these objectives. It should also identify the stakeholders, their roles and their expected contribution towards meeting these aims, and direct decision-making. Its formulation should act as a springboard for discussion at national level, creating mechanisms and pathways bringing all parties together in a unified approach and direction.

The study results consistently demonstrated that there was a manifest disconnect between the governance system and practising health care professionals. These had little knowledge of the indicators which weighted decision-making, or the mechanisms used to take these decisions. They felt that they had minor or close to nil influence in this sphere, which effectively discouraged any attempts to try. Rather than obtaining information inherently from their work environment, they resorted mainly to medical representatives and international journals. Prescribers found it hard to provide an explanation to patients who could not access their medication through the NHS, since they themselves felt that the system was discriminatory. There can be little doubt that the feedback of these protagonists would be vital to the successful attainment of policy objectives. It would also impart a sense of ownership of, and involvement in, the system.

Clearly defined roles and responsibilities enable synergistic multi-disciplinary teamwork. Assigning responsibilities supporting Access would mitigate action likely to affect ATM

negatively, whilst maximising actions with positive outcomes. All partners who form part of policy implementation should be identified, their fundamental role and responsibilities should be recognised, and their knowledge and experience should be harnessed. These protagonists include health care professionals, financial representatives, patient groups, non-governmental organisations, regulators, professional bodies and the industry.

### 4.2.3 The Components of Policy

Admittedly, a National Access Policy which embraces the principles of equity, transparency, and inclusivity, whilst also equilibrating financial, social and commercial elements in line with health needs, is not easy to achieve. The strategies supporting its implementation should ensure that one imperative (such as Access) does not stifle others (such as sustainability), but that a reasonable balance leading to expected outcomes is managed and maintained. Unfortunately, we have examples of programmes intended to curb costs through encouraging generic prescribing that had the unplanned effect of reducing Access to, amongst others, anti-psychotic therapy at a time when most health systems are prioritising mental health.

Such experiences reinforce the requirement for feedback, monitoring and evaluation to be a key component of medicines policy. The findings of this study showcased diverse market failures which left patients and health care professionals seeking quick-fixes to address the immediate problem, sometimes conscious that their actions could lead to other complications. There was consensus that these failures were being experienced with increasing frequency. Whilst permanent solutions should be the long-term objective, interim,

pragmatic and coordinated means of resolving these problems should be introduced in the meanwhile. This forms an important element of an Access policy, which should explore and establish options for plausible solutions.

An effective policy should incorporate the principles of rational prescribing and use, and target the development of performance indicators which measure progress, impact and outcome. Monitoring and evaluating policy outcomes also enables insight into how the organisation of pharmaceutical care impinges on ATM and how it may be remodelled to condition Access. The pathway between the grant of a marketing authorisation and entry onto the positive list was flagged as deserving specific consideration. The positive list is viewed as the major gatekeeper to ATM. Its operation also has the potential to influence market characteristics significantly, consequently impinging on Medicines' Access. The research findings identified that this was particularly the case for the Small States.

This systematic and structured methodology can be further built upon through the voluntary exchange of information with other Member States, comparing different utilisation modalities and outcomes. Besides identifying diverse policy trajectories, it would also enable recognition of commonalities between the Member States with a view to initiating cooperation and improved harmonisation in future.

The case for more and better data can never be over-emphasised and is key to sustaining transparency and endorsing the workings of policy. Assembling a strong evidence base informs decision-making and allows scrutiny of the underlying rationale. Without

transparency, stakeholders fail to understand and follow policy decisions, evaluate the data for its strengths and weaknesses, or improve on it through further research. Effective policy should keep evolving with time, relying mainly on robust evidence and research to do so.

Stakeholders pointed to an insufficiency of evidence relating specifically to ATM at a national level in most countries. Moreover, the divergence in Access between Member States is mirrored by a similar divergence in data which is scarcer in the smaller territories.

### 4.2.4 National Policy and EU Law

The relevance of publicly available national policies espousing ATM was questioned by a number of stakeholders who considered it to be overtaken by EU legislation. However, whilst this is certainly correct insofar as the quality of medicinal products is concerned, the EU cannot set policy targeting ATM at Member State level. European regulation focuses mainly on the establishment and functioning of the internal market. Outside this framework, EU legislative action is difficult to achieve politically. This is due in large part to the significant diversity in the organisation and provision of health care delivery, as well as in the considerable economic differences and patterns of funding between Member States. It would be difficult for a pan-European policy to accommodate this wide spectrum of divergences. As things stand, health remains a Member State competence. This means that the policies on which the service is founded and operates falls outside the scope of EU law, and cannot be effectively pursued by EU policy-makers in view of the constraints placed by the Treaty which denies them the explicit competence to do so. This principle was reinforced by

President Juncker in a Mission Letter[55] in 2014 to the Commissioner for Health, emphasising that setting policy on health systems is the remit of the Member States.

Therefore, whilst the quality of medicinal products is assured through the European legislative framework, the primary focus for ATM must reside at Member State level and should be reflected in, and discharged through, policies set at national level. This is not to say that the EU has no role to play in the endeavour for ATM but that the balance of incumbency tilts towards the Member States.

Despite a degree of confusion relating to this facet of policy, stakeholders were largely in agreement regarding the practical implications of EU membership on the NHS. The pharmaceutical Acquis resulted in a reform of national pharmaceutical legislative frameworks underpinning the marketing of medicinal products and medical devices and specific areas of Good Practice such as manufacturing, distribution, and pharmacovigilance.

This was perceived as an opportunity to raise standards, strengthen the relevant institutions and clarify roles and responsibilities. However, in several Member States, the system of health care delivery remained essentially unaffected and unchanged. In some cases, this gave rise to a disconnect between the provision of pharmaceutical care and the EU framework, for example in the procurement of medicinal products, with possible repercussions on ATM. It also underscored gaps which could not easily be transposed into the existing NHS infrastructure, such as pharmacovigilance and the Falsified Medicines Directive. These

[55] Juncker, J. Mission Letter to Vytenis P. Andriukaitis Commissioner for Health and Food Safety 2014 [Internet]. November 2014 [cited 2021 Apr 17]. Available from: https://ec.europa.eu/archives/juncker-commission/docs/andriukaitis_en.pdf

deficiencies can only be appropriately addressed through a complete appraisal and overhaul of the organisation of pharmaceutical services, building on the precepts of the European framework and defining ATM as a focal point.

### 4.2.5 Policy and Change

Although it was felt that change and improvement were much needed, stakeholders considered this to be improbable under the current circumstances for multiple reasons. Foremost amongst these was the intricate nature of health care provision with the innumerable pressures, constraints and exigencies under which it operates. A reform of this import was also anticipated to encounter stiff resistance from the actors and interested parties concerned. Stakeholders were dubious that these difficulties could be countered effectively, particularly when considering competing priorities, some of which were prescribed by the EU. It was noted that it was often EU-driven obligation, lacking in these circumstances, which provides the catalyst and mechanism for implementing change.

Ambivalently, stakeholders were mainly resistant to further Europeanisation of the pharmaceutical domain or indeed of the whole dimension of health care provision. This will be discussed further in the following section of this chapter.

There was a strong belief that current disparities between the Member States in this area were too great to allow collective and homogeneous development at a pan-European level: it was felt that the consequences to some Member States would be detrimental were this to occur.

However, it was acknowledgement that EU integration influenced the delivery of pharmaceutical services significantly, albeit indirectly, and that this manifestly created tensions, including in relation to ATM, which require resolution.

This ambiguity or conflict between Member State's organisation of health care and EU precepts is evidenced by a progression of seminal judgements made by the European Court of Justice in this field. This concatenation of precedents, set in areas such as reimbursement of health care costs and patient mobility, can be arguably viewed as providing policy direction in health care (Mossialos and McKee, 2001; McKee and Mossialos, 2006; Permanand et al., 2006). It is unfortunate that it has fallen to the Court to fill gaps arising from EU-Member State mismatch since it is usually the atypical cases which trigger these rulings.

It is envisaged that a national policy process would be a judicious and opportune mechanism with which to address such shortcomings with a particular focus on ATM. It would also provide the impetus and direction for future change where this is expedient. Once a policy platform that is better aligned to EU rules has been created, it will evolve such that it is able to absorb new developments. It would also enhance awareness and understanding of ATM and its determinants, and would identify commonalities between the Member States which have the potential to act as a springboard for cooperation in this field.

## 4.3 European Regulation and Access to Medicines

The primary focus of the EU's pharmaceutical Acquis is to protect public health by regulating the quality, safety and efficacy of medicines on the single market to an appropriate standard. It does so whilst supporting a competitive and innovative pharmaceutical industry. This is in line with the Commission's Pharmaceutical and Industrial Strategies[56], which both recognise the importance of this sector as a major pillar of the European economy. This complex framework is managed by EU-wide systems which facilitate trade under the liberal market.

### 4.3.1 The Effects of EU Integration

There was consensus amongst stakeholders that EU integration had a positive net effect on health care, and more expressly in the pharmaceutical arena. Several beneficial consequences were cited, amongst them the establishment and enforcement of scientific standards, the attendant specialisation of professionals working in the field, the external scrutiny of norms and procedures, and the objective measure of outcomes. Financial and technical assistance in networking, cooperation, training and capacity-building were seen as major advantages. The price for the transformation of the pharmaceutical sphere included an inevitable increase in bureaucracy and the pressure of keeping up with the dynamic developments in this field. Initiatives at national level were often stifled by an overwhelming EU-priority agenda, which did not necessarily translate into advances in patient care, particularly in the case of ATM.

[56] European Commission. Pharmaceutical Strategy for Europe 2020 [Internet]. 2020 [cited 19th April 2021]. Available from: https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf

This problem is much more pronounced in the Small States, which shoulder a similar administrative burden with significantly constrained resources.

The architecture of the pharmaceutical arena was perceived as leaning too strongly towards the market-oriented, commercial component, unlike the non-commercial element which was not similarly impacted. Positive EU effects such as the establishment of clear standards and goals, transparency, accountability and outcome appraisal did not extend to this latter segment of the organisation of pharmaceutical care.

### 4.3.2 The EU Health Mandate

Predictably, medicinal products and medical devices, both highly valuable goods of commerce, are profoundly influenced by the maxims intrinsic to the liberal market and the free movement of goods, which are EU founding principles. At the other end of the scale, however, is the EU's health mandate, which affirms its commitment to a high level of health protection for its citizens. This obligation was the cornerstone on which the current European health-related infrastructure was built, including crucial institutions such as the Directorate for Health and Consumers (DG SANCO) and the European Medicines Agency (EMA). The attestation to public health protection is assumed to equilibrate the inclination towards the industry. This inference was contested by stakeholders who saw the industry as having optimal control of the pharmaceutical domain, resulting in tensions between essentially conflicting non-commercial (health) and commercial (industry) goals.

It was acknowledged that the Treaty mandate has led to a number of achievements, notably in the development of competences which support, coordinate and fortify the Member States, resulting in value-added outcomes. However, it has not succeeded in making health, and therefore pharmaceutical care, a central EU objective, thus allowing goals such as ATM to become missed opportunities at the mercy of other interests. There is the perception that EU action in this context has so far been proposed in spill-over fashion rather than being adopted holistically and proactively.

The leading role that has, of necessity, been taken by the European Court of Justice to provide an interpretation of the Treaty and relevant legislation, attests to the gaps that exist in the field of health care. Since the Court's rulings, even when pertinent to health issues, must be grounded in the principles underpinning the market and free competition, subsequent action to such judgements is often followed up by the Directorate General for Internal Market and Services, and by politicians (Mossialos et al., 2010). This reflects the sovereignty of the single market over social protection and the weakness of the EU's heath mandate. The result is a patchwork of measures, legal or otherwise, which do not take into account the specificities of national health systems, but which have a profound influence on them, and for which the Member States must contrive methodologies which are consistent to EU dogma. Meanwhile, the pharmaceutical industry selects research and development priorities, judges which markets to enter, chooses when to enter them and determines which monopoly prices it can more-or-less charge, all decisions driven by business interests. The major challenge to ATM identified by EU-based stakeholders was the strength and dominance of the multi-national industrial lobby, which was deemed difficult to overcome.

### 4.3.3 The Small States

According to Briguglio (Briguglio, 2016), the Small States of the EU are those with a population of circa 3 million or less. The 7 countries which qualify under this definition are Malta, Luxembourg, Cyprus, Estonia, Latvia, Slovenia and Lithuania, with Malta being the smallest by both surface area and population. The smaller domestic markets of these Member States restrict them from reaching a critical mass of profit to the industry. Contrarily, the inherent limitations of economic diversification make them heavily reliant on international trade. These characteristics render the Small States vulnerable to singular constraints and challenges not faced by larger countries. The situation of Malta and Cyprus is further aggravated by virtue of the inevitable logistical problems faced by islands.

The Small States are thus particularly vulnerable to the economic model under which the pharmaceutical market operates. There was agreement that although the pharmaceutical Acquis establishes a common benchmark throughout the EU, the way it affects the Member States in terms of ATM varies significantly. This divergence is more pronounced in the smaller territories whose specificities magnify barriers to Access. The investigation into dispensing pharmacists' viewpoints revealed that approximately one third implicated the regulatory regime and a lack of interest from the industry in smaller markets as major barriers to Medicines' Access. In corroboration, stakeholders referred to the comparatively restricted range of medicines placed on these markets, the difficulties faced in obtaining medicines for the NHS, and the dearth of competitor products leading to market consolidation and dependence. The non-availability of alternative preparations not only restricts choice but also amplifies a susceptibility to shortages. Prices are generally higher, in part due to the lack of

competition and lower negotiating power but also stemming from the small market size requiring lower volumes and, therefore, generating lower profits. Stakeholders and practising health care professionals were united in their concern regarding advanced and innovative therapies whose access is particularly compromised. Although financial considerations and national health system pathways may potentially aggravate this issue, the overarching problem remains the general disinterest from the industry in the smaller markets.

As a consequence of these market characteristics, the Small States face fundamental obstacles relating to two key pillars of access: availability and affordability. Medicines which have been granted a marketing authorisation through a centralised procedure, but are still absent from the market, substantiate this failure. In this case, whereas the Member State has contributed to the process and there is nothing to stop the product from being marketed, patients are still being denied access to it. This situation does not bode well for the future of ATM in the Small States when considering that this procedure, whose use is intended to continue growing, is the instrument designed to facilitate the European pharmaceutical market into a single market. Stakeholders voiced their frustration that efforts by Competent Authorities and academics to delve into this issue were rebuffed by the industry. Given that every Competent Authority must commit its resources towards granting the marketing authorisations, it was felt that the EMA could lend its support by asking prospective Marketing Authorisation Holders about their intentions to market in the territories.

The United Kingdom's departure from the EU (BREXIT) has posed a further challenge in medicines' availability in the Smaller States, particularly Malta. As a consequence to

BREXIT, medicines coming from the United Kingdom have now to undergo an importation process in order to enter the EU market. This includes the requirement for re-testing and certification by a Qualified Person. Supply chains have had to be reorganised with the products going to an importer, rather than a wholesale distributer's facility. The repercussions to BREXIT encompass pharmaceutical companies in third countries which previously used the United Kingdom as a first port of call. These changes, with their additional costs and complexities, have hit the smaller and less profitable markets particularly badly. Malta has been more negatively impacted than most due to its relatively greater reliance on pharmaceuticals sourced from the United Kingdom. Being an official second language, packaging in English is permitted on the Maltese market, bypassing the need for repackaging for a small market, already unattractive to the industry.

The issue of packaging in the country's national language may be seen as an additional ATM obstacle in the smaller markets. This may be partially resolved by the inclusion of QR codes on medicines' packaging which would link to the Competent Authority or industry webpages. EU regulators agree in principle to the use of QR codes as a means of updated information provision. However, their use to substitute statutory packaging data has yet to be sanctioned[57].

BREXIT was one of the areas dealt with during Malta's presidency of the EU in the first six months of 2017. Conscious that the perennial problem of medicines' availability (due to its

[57] The Co-ordination Group for Mutual Recognition and Decentralised Procedures – human. CMDh Position Paper on the Use of QR Codes to Provide Information about the Medicinal Product. April 2016 [cited 2023 Nov 01]. Available from: https://www.paint-consult.com/fileadmin/editorial/downloads/guidelines_behoerden/packungsbeilagen/CMDh_position_paper_use_qr_codes_2016.pdf

limited market) would be aggravated by BREXIT, Malta worked towards the Valletta Declaration. This initiative aims to enhance Member State cooperation and joint negotiation with the industry on medicines' procurement and pricing[58].

Undoubtably, EU efforts to promote ATM through initiatives such as PRIority MEdicines (PRIME) Scheme[59], Adaptive Pathways[60] and Conditional Marketing Authorisations[61] are commendable in principle. However, in practice, they are of little use to the smaller territories unless there is a change in commercial bias against them.

Stakeholders expressed their disappointment that the constraints and ramifications under which the Small States operate are not sufficiently considered or understood at EU level. Indeed, there is the expectation that formulas effective in other countries should produce similar results in the Small States. This is possibly exacerbated by the fact that key EU decision-makers often come from the larger countries. Moreover, specific needs pertinent to Small States are often overlooked and impact assessments of incoming legislation do not generally account for the singular challenges faced by these territories particularly in relation to ATM. Stakeholders were also disheartened that oratory and documentation regarding ATM at EU level had generated little, if any, tangible improvements to patients so far.

[58] Central Procurement & Supplies Unit, Ministry of Health, Malta. The Valletta Declaration: Good practice in medicines procurement and negotiation to improve access to effective Treatment and support sustainability of healthcare systems. June 2021 [cited 2023 Nov 01]. Available from: https://www.ipaac.eu/res/file/roadmap/id005.pdf

[59] European Medicines Agency. Prime: a two-year overview. May 2018 [cited 2023 Mar 01]. Available from: https://www.ema.europa.eu/en/news/two-years-prime

[60] European Medicines Agency. Adaptive pathways. No date. [cited 2023 Mar 01]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways

[61] European Medicines Agency. Conditional marketing authorisation. No date. [cited 2023 Mar 01]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation

### 4.3.4 Europeanisation of Health and Pharmaceutical Systems

In considering a wider role for the EU, there is virtually no interest in radical change to the health care delivery models adopted by the Members States. Many of these reflect the values of the country and embrace its social and medical cultures. They have also been adapted to the domestic economic realities and priorities. The majority of stakeholders believed that the EU approach to health so far has not been encouraging and that, unless there is a palpable change in direction, Europeanisation of health systems will have mostly negative consequences.

In the pharmaceutical sphere, the situation is paradoxical. Stakeholders were categorical that scientific support was a major EU contribution. Other assets included the sharing of information and experiences, and the opportunities for cooperation and partnerships available. These positive effects are counter-balanced by a number of negative experiences, some of which have been discussed in previous sections of this chapter. Others include a perception of growing and unwelcome EU fiscal involvement, and the thorny problem of unmet expectations, particularly where ATM is concerned. The gap between EU rhetoric and discernible national gains was questioned by most stakeholders: a lack of continuity between rotating presidencies was flagged as one cause and a lack of resilience to engage was highlighted as another. Long-standing pledges to harmonise pricing and HTA, both basic and key elements of ATM, have not come to fruition, making further Europeanisation of the pharmaceutical sphere highly contentious.

Conversely, there was recognition that the introduction of EU obligations would constitute the means most likely to be successful in instigating change in this sector: scepticism however centred around what form this change could take in order to bolster ATM. There was pragmatic acceptance that Court rulings will inexorably continue influencing health and pharmaceutical systems. Evolving legislation such as the patients' rights and cross-border directive (2011/24EU) will intensify this effect. The study results reinforced the notion of unpreparedness in this regard, and illustrated that, at national level, structured mechanisms to sustain this obligation are not in place. These issues coupled with a tightly, but only partially, regulated pharmaceutical domain led some stakeholders to consider early EU intervention targeting an integrated revision of this sector as an option.

However, despite a degree of ambivalence, the general consensus was that Europeanisation of the pharmaceutical arena should be stalled until the EU's current approach changes. Meanwhile, subsidiarity should remain.

### 4.3.5 The EU's Role in Instigating Change

There is flexibility in the principle of subsidiarity in that, although EU action may not supplant, it may complement that of the Member States. This strategy lends itself to the better realisation of ATM, which is dependent for its success on congruent and synergistic effort from both the Member States and the EU. It also has the merit of safeguarding subsidiarity, whilst allowing the EU to take a softer approach which builds on its positive attributes.

Rather than using regulatory compliance as a platform for change, this mechanism relies on encouraging conjoint action and facilitating cooperation and partnerships between the Member States in a coordinated and structured fashion. It is undeniable that the Commission has succeeded in shifting the narrative towards ATM, placing it firmly on the EU agenda. Equally true is the fact that few inroads have been made into dismantling access barriers and a change in the approach to ATM is advocated. It is proposed that this change takes the form of extending the EU's current commitment of health protection to that of health promotion in the context of ATM. This more proactive and visible role should enable effective levelling of the current balance of priorities squarely towards health and social welfare goals.

## 4.4 A European Approach to Access to Medicines

National medicines policies which endorse the goals and organisation of pharmaceutical services and which support their direction and development have been identified as a valuable tool in the attainment of ATM. There can be no doubt that the ideal scenario in the long-term is one where all the Member States will adopt a pan-European framework supporting the ATM decision-making process. This should be complemented by EU support in areas where co-ordinated action and networking enhance outcomes. To achieve this objective, a strategy of gradual cohesion and harmonisation is necessary, which takes into account each Member State's unique model of health care delivery, but which simultaneously provides scientific objectives and guidance which optimise ATM. To address this issue, this research identified domains which may be integrated into a facilitating framework for the formulation of pharmaceutical policy.

### 4.4.1 The Case for a Holistic Framework Supporting Access to Medicines

There is universal agreement that access to appropriate therapy is a crucial element in the continuum of health care provision (Official Journal of the European Communities, 2000; World Health Organization, 2016). The study results as well as the literature (WHO, 2004) corroborate that decision-making which is not targeted or evidence-based in this regard risks sub-optimal health outcomes as well as inefficient financing modalities. Regrettably, Europe's health care systems are currently challenged by inequitable and reduced access, a situation which seems set to deteriorate further as more complex, advanced and costly medicines surge through the research and development pipeline (Hasan et al., 2018; Jongh et al., 2021; European Federation of Pharmaceutical Industries and Associations, 2022; World Health Organisation. European Region, 2022). The literature (Afzali et al., 2019) and the findings of this study are consistent in endorsing the need for a structured framework, with specific indices, aiming to support medicines' accessibility. Current research addressing paradigms for improving ATM does not generally follow a systems approach (Afzali et al., 2019), but rather focuses on individual obstacles or causes such as affordability and availability (Costa-Font et al., 2007; Jiang et al., 2013; Wahlster et al., 2015) or is confined to a disease type (Cummings et al., 2014) or patient group (Davidová et al., 2008).

Addressing single parameters in isolation does not necessarily lead to an overall improvement in access to effective medication, rationally used, with validated value to patient outcomes. For instance, considering two of the most pertinent ATM indices as examples: the benefit of safeguarding the *affordability* of medicines whose therapeutic value

is unproven is, at best, dubious; and similarly, assuring the *availability* of expensive products whose clinically meaningful benefit is lacking in evidence undermines the delivery of effective health care. Addressing measurables comprehensively through an interlinked and structured system would inaugurate a holistic approach to ATM.

### 4.4.2 The European Marketing Model

In particular, EU regulators have pursued a strategy of accelerating the development and authorisation of medicines as the primary tool towards improving ATM. In this context, swifter access is considered in isolation as a distinct determinant. This thinking is based on the premise that the new product is superior to existing therapies, and the presumption that faster market entry (for example, through accelerated pathways and conditional marketing authorisations) will lead to improved health outcomes. This research highlights the scepticism with which stakeholders regard this initiative, which they feel brings more advantages to the industry than it does to the majority of patients. A review of the literature indicates that this viewpoint is justified, with less than one third of medicines approved through expedited pathways judged to have high added therapeutic value (Wieseler et al., 2019; Hwang et al., 2020; Vokinger et al., 2022). Additionally, participants of the focus group pointed to the fact that stipulated post-marketing studies often do not materialise, a well-known problem which regulators seem unable to rectify.

Most studies which retrospectively examine the added benefit of new therapies over existing ones (Davis et al., 2017; Mintzes and Vitry, 2019; Hwang et al., 2020) are restricted to a specific group of products, or to a defined time-period, and do not therefore provide a

systematic review benchmarking the therapeutic value that these medicines actually bring to Europe's health systems. They do however consistently prognosticate the necessity of reforming the current approach. Certainly, the overall sentiment amongst the stakeholders of this study was that expedited approval mechanisms are of questionable benefit in achieving a step change in patient outcomes. Furthermore, they constitute a higher probability of safety concerns occurring later on. Such medicinal products introduced into publicly funded health care systems may cause harm to individual patients, waste vital resources and undermine the delivery of equitable and affordable care. The clear message emerging from this research is that the focus should be shifted towards better, not just faster, solutions which more ably address the priorities of health systems.

To align the industry and health services to meet current challenges, it would be wise to encourage the development of more effective and sustainable therapies and to discard medicinal products which do not contribute tangibly to improved health outcomes. In the aftermath of the COVID-19 pandemic and in the throes of escalating prices that have only worsened individuals' health, informed choices are critical in maximising the potential which new therapies may offer. A starting point would be to radically overhaul the process through which medicines come onto the market in the Union. There was universal agreement amongst the participants of the focus group on the criticality of moving towards a central European marketing model which is fit for purpose in terms of ATM. The ongoing pharmaceutical legislative review by the Commission planned for adoption in 2023[62] provides an excellent opportunity to develop an enabling framework for this purpose.

[62] Antunes, L. Towards a new EU pharmaceutical strategy. Think Tank European Parliament. [Internet]. 2022 [cited 2023 Jan 5]. Available from: https://www.europarl.europa.eu/RegData/etudes/ATAG/2022/737129/.EPRS_ATA(2022)737129_EN.pdf

One vital aspect of this modified centralised authorisation which was consistently raised by stakeholders is that it should be conditional to marketing the product in all the member states. It is encouraging to note that the Commission has recently been deliberating this possibility [63] reflecting awareness that EU marketing strategies are not in line with ATM. The problem of pharmaceutical companies being mainly focused on the bigger European markets was persistently raised by stakeholders as a major weakness inherent in the current system. Presently, negotiations with the industry centre around a two-year period for placing the newly-authorised product on the market of most (but not all) Member States. The lack of a blanket approach does little to reassure stakeholders from the smaller territories, who highlight this as a loophole which effectively renders the legislative requirement out of scope for equitable medicines' access. On the other hand, the unresolved problem here remains pricing, which currently appears to have moved off the European agenda, but which is inevitably linked to the reality of launching a new medicinal product onto the market.

Another key ingredient for a new marketing model's success would be to close the yawning gap in the evidence-base attesting the benefits and risks of new therapies. Increasingly, data which has supported medicines' approval has been revealed to be inadequate after the product is placed on the market (Eyding et al., 2010; Loder and Godlee, 2010; Trish, 2010) and it is urgent that the integrity of this clinical evidence-base be reinstated. Health technology assessors involved in this study spoke of the mounting pressure they face to approve

[63] Fabre, J. 2021. EU considers reform of general pharma law. Out-law News [Internet]. 2021 [cited 5th January 2023]. Available from: https://www.pinsentmasons.com/out-law/news/eu-considers-reform-of-general-pharma-law

medicinal products whose benefit is doubtful. Therapies approved in this way expose patients to low level care that does little to improve their health outcomes, and indeed may actually harm them. This situation creates unnecessary conflicts between regulatory approval and health system priorities, with policymakers pointing to the difficulty of ensuring cost-effective health care provision in this environment. Stakeholders overseeing the managed entry of medicines into national health systems deplored the fact that biased evidence of this nature may then be used for such products to be accepted into formularies. The literature concurs, proving that flawed evidence has been found to form part of marketing strategies to promote medicines' use (Wieseler et al., 2019). Even when Cochrane Meta-analyses or other retrospective studies demonstrate that a substantial number of products are of little or no therapeutic value, they continue to be used since these findings do not inform the medicines' authorisation.

Tough decisions must be taken to elaborate regulatory processes that are scientifically robust, and which undertake best-practice due diligence in judging clinical evidence. It is also necessary to develop norms and guidelines to achieve convergence with the Clinical Effectiveness Assessment component of Health Technology Assessment (HTA), which should resolve the growing tension between regulators and health technology assessors. The latter are often placed in the invidious position of acting as health system gatekeepers and refusing the entry of products that have been granted marketing authorisations without sufficient evidence of clinical benefit. HTAs are fundamental in determining the add-on value a medicinal product may bring to the health care system leading to best practice decision-making in terms of its optimal rational use, its pricing and reimbursement conditions and its

budgetary impact. Logically, the evaluation framework should be seamless for regulators and health technology assessors and the data collated during the drug development process should be such as to satisfy the requirements of both. The evidence from phase III randomised clinical trials to prove efficacy and safety should be able to be used in parallel to collect data for the HTA. In this context, a step in the right direction has been taken with the recently adopted legislative amendment[64] which is in-line with the recommendations of this study. It aims to provide pan-European support and co-ordination in the clinical assessment of health technologies and should mitigate the long-standing discordance in the approaches by the Member States in this regard. It is, as yet, too early to assess the workings of the co-ordination group set up for this purpose since only administrative issues have so far been tackled. However, an agenda has been planned and it will be interesting to examine future implementation once the amending Regulation has been detailed.

Beyond data requirements, the regulatory and HTA specifications should be synchronised since regulatory decision-making has huge impact on health care systems. Demonstrating value to ensure optimal market access should be integrated into the drug development process and the conduct of active controlled clinical trials should be made mandatory. Stakeholders involved in HTA pointed out that many of the surrogate outcomes used for regulatory approval are either poorly correlated with, or not tested against, actual outcomes. It is problematic that the EMA often bases approval decisions on uncontrolled study designs, or surrogate end-points, when these are not held to be clinically reliable indicators. Neither are

[64] European Commission. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on Health technology assessment and amending Directive 2011/24/EU [Internet]. Official Journal of the European Union [2023 Jan 5]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R2282&from=EN

invalidated biomarkers whose outcomes are concluded to be 'reasonably likely,' a far cry from 'proven.' The situation is compounded further when a medicinal product lacking robust evidence of efficacy is then used as a comparator for new products.

To achieve optimal market access it is critical that therapeutic value and added therapeutic value are well-evidenced, and regulators should work together with health technology assessors to ensure that medicinal products are only approved using methodologically rigorous designs and procedures in this regard. In unavoidable cases where the evidence is not strong, post-marketing studies with clinically meaningful outcomes, which are patient-centred, should be enforced. Moreover, the emerging data should be proactively shared with health care professionals. The concept of evidence-based medicine is intrinsically bound to the future of ATM. It will be largely determined by the sources of information that we accept as valid, and highly influenced by the regulatory landscape we craft.

### 4.4.3 A Facilitating Framework Supporting Access to Medicines

There is clearly a role for the EU to motivate Member States to formulate national policies which target access to effective medication as a core principle. Various tools and approaches may be used to attain this goal and each state should have flexibility in selecting and pursuing the modality most fitting to their needs and circumstances. Concomitantly the EC is best placed to create a generic systems approach which targets common ATM indicators and champions their furtherance. This strategy will allow progressive harmonisation throughout the Union through the creation of a platform which promotes constructive dialogue and

collaboration between stakeholders. By co-ordinating a facilitating framework which may be customised by each Member State, the EC may instigate the generation and exchange of information and the development of scientific norms and principles. The validity of this model depends in large part on reliable data, objectively scrutinised.

Figure 4.1 portrays how a European Access Framework may support the entry and rational use of medicinal products into the national health system. Member State adaptation of the Access Framework should be delineated by national policy. The purpose of this approach is to embed ATM catalysts in key positions at different levels of the health system and to identify interconnections with ATM constraints when they occur.

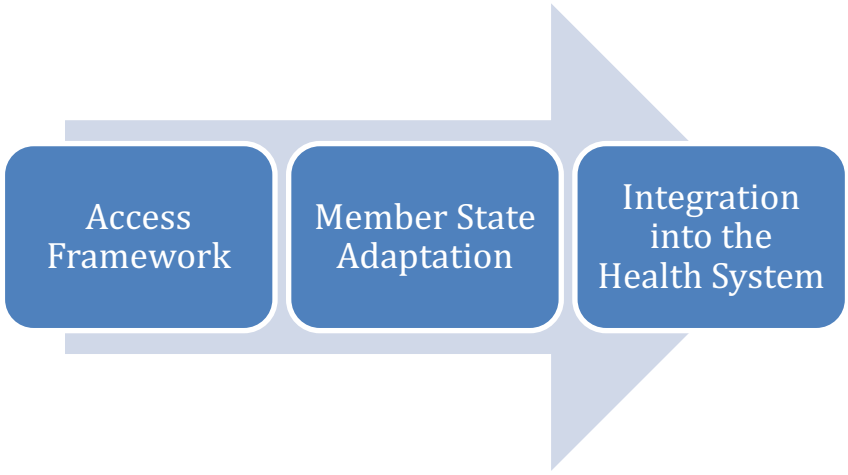


*Figure 4.1: The Access Framework within a European Model*

The findings of this research highlight that the Access Framework should incorporate not only medicines' entry and utilisation but should also include monitoring and evaluation of the actual outcomes. Through this study, ATM indicators were identified and categorised into four distinct dimensions or domains, as presented in Table 4.1.

| The Access Framework | |
|---|---|
| **Domain** | **Indicators** |
| Uptake | • Pricing / Reimbursement<br>• Forecasted cost-effectiveness / Therapeutic Value<br>• Prospective public health gains (health strategy, data regarding prevalence)<br>• Projected budgetary impact<br>• Affordability / Sustainability<br>• Expected clinical effectiveness, forecasted cost-effectiveness<br>• Prospective public health gains (therapeutic value)<br>• Horizon scanning followed by HTA |
| Utilisation | • Availability / Shortages<br>• Rational use: protocols / national treatment guidelines<br>• Rational prescribing<br>• Dispensing / Counselling<br>• Public Campaigns (educational material)<br>• Feedback from health care professionals and patients<br>• Involve patient organisations |
| Evaluation | • Prescribing or dispensing database incl. patient numbers<br>• Actual reimbursement and expenditure data<br>• Utilisation studies targeting evidence-based treatment outcomes<br>• Utilisation of real-world data |
| Re-Appraisal | • Audit results: do these correspond to the expected cost-effectiveness and public health gains?<br>• Does the medicinal product satisfy the Access Framework indicators?<br>• Should treatment guidelines and protocols be re-appraised?<br>• Audit results: do these correspond to the expected clinical effectiveness, cost-effectiveness, therapeutic value |

*Table 4.1: The Access Framework: An Approach to the Entry and Utilisation of Medicinal Products in a National Health System*

Each domain denotes a type of activity which collectively, if staged and linked chronologically, enable a continuous evaluation and re-evaluation of the medicinal product. This process, which delineates the Access Framework, is shown in Figure 4.2. It

demonstrates how the Framework may be utilised to support the rational use of medicines and effective outcome measurement.

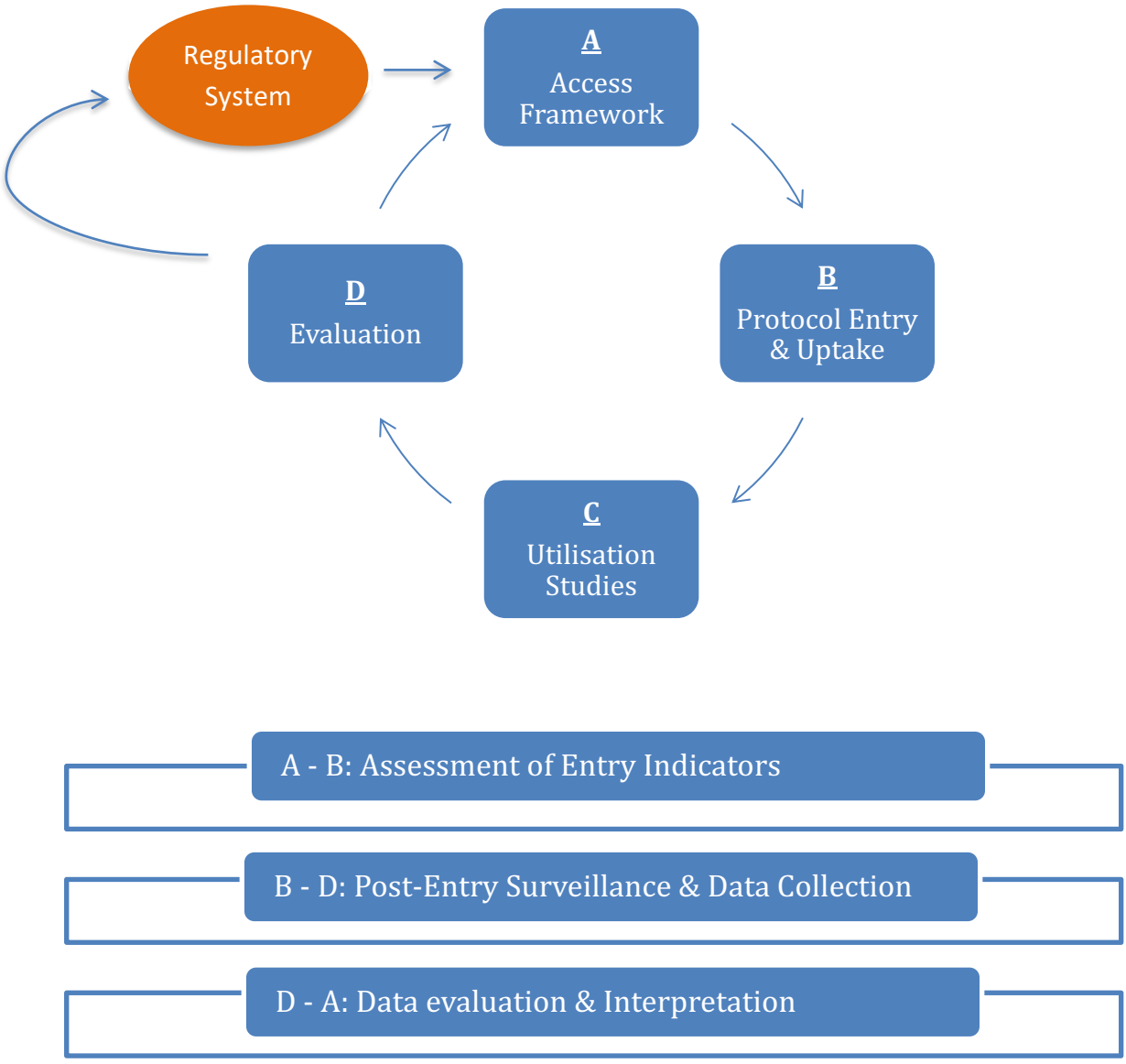


*Figure 4.2: Life Cycle of the Access Framework*

Importantly, the focus group validated the proposed framework, affirming the importance of evaluating and monitoring all aspects of ATM using purpose-specific tools or indicators. Grouping these indicators into systematic domains of action facilitates the flexible utilisation of the framework. This novel holistic approach has the advantage of addressing the entire pharmacotherapy lifecycle from assessment and acceptance into the NHS up to the rational use of the medicinal product. In addition, the framework incorporates the concept of post-entry outcomes evaluation, to validate (or otherwise) the therapy's effectiveness and added therapeutic value. This aspect was cited by the focus group as a major strength of the Access Framework. It grants the opportunity to raise the evidence bar for clinically meaningful benefit to ensure that medicines with proven effectiveness are prioritised and to improve the quality of health care. More work is required to generate evidence that systematically examines the magnitude of benefit that approved therapies bring to patients.

In examining the strengths and opportunities offered by the Access Framework, several defining features stand out. One major characteristic is that it reinforces the fundamental precept of data-generation and patient relevance whilst bridging the medicinal product pathway in pharmaceutical care. It therefore affords the opportunity of extensive outreach at all levels of the health system, bringing stakeholders of different expertise backgrounds together to enable the formulation of policy informed by evidence. In so doing, it propounds gradual adaptive process development, another perceived strength. It enables the identification of access barriers or, conversely, drivers, opening up the prospect of improving future performance and enabling Member States to take reasonable measures to facilitate ATM. Another advantage of the Access Framework lies in its potential to increase pan-

European homogeneity in this area by bringing the Member States together and by the cohesion of, and adherence to scientific standards.

A precondition to attaining this goal would be the setting up of a central EU entity tasked with co-ordinating the Access Framework and fostering solidarity in tackling growing access inequalities within the Union. It would also be effective in the broader endeavour of bolstering the sustainability of European pharmaceutical care. A major role would be the co-ordination of network channels to facilitate the collation, analyses and sharing of high-quality data and to develop reliable, timely and transferable information. Such an entity would have the capacity to harness and secure access to the best available competence in Europe, ensuring the translation of information into best-practice guidance. It could also develop improved communication through efficient pathways and by specifying relevant terminology into MedDRA (Medical Dictionary for Regulatory Activities). This would align definitions (e.g. unmet needs) with the regulatory domain and underpin the scientific essence of the framework. By leveraging alliances and partnerships in strategic areas, it could enable the collaborative generation and evaluation of evidence to optimise the scientific quality of decision-making. Crucially, it could support the Access Framework by working closely with other EU agencies which share mutual interests, such as the European Reference Networks (ERNs), EUnetHTA (the European Network for Health Technology Assessments) and the EMA, particularly its Health Care Professionals Working Party (HCPWP) and the Patient's and Consumer's Working Party (PCWP) and of course the Committee on Human Medicinal Products (CHMP). Other resources which could bring add-on value to the Access Framework may include the EMA Shortages Catalogue, the Joint Negotiation and Procurement of

Medicines Group, the European medicine price database (EURIPID), Horizon Scanning fora and Data Analysis and Real World Interrogation Network (DARWIN EU®). The latter could support the Access Framework significantly as a source of validated real-world data (RWD) which allows insights, not possible from pre-approval clinical trials. Its analysis generates real-world evidence (RWE) from heterogenous populations. Notably insufficient RWD was cited as one of the weaknesses of the Access Framework. Aside from quantity, data quality is another on-going concern. Despite initiatives to construct a common data model which enables standardised analytics to generate reliable evidence, consistency and completeness of data have not yet been achieved. It is hoped that by 2026 DARWIN EU® will be fully operational in meeting regulatory needs. However, more work would need to be done to curate it to the requirements of the Access Framework.

The pharmaceutical industry featured as both a potential weakness of, and a threat to, the framework. There can be no doubt of the industry's strength as a lobby group. It is also a fact that the objectives of these private companies differ fundamentally from those of health organisations and from the way they perceive patient benefit. It has been shown that the industry exerts considerable influence on politicians, policy-makers, health care professionals and even patient groups (Goldacre, 2012; Moberly, 2019; Salisbury, 2019) so that arrangements are designed to the company's advantage. It comes as no surprise therefore that the major threats identified to the Access Framework revolved around this issue, and the expected backlash from these quarters. A reluctance by politicians to abrogate power and to commit themselves to national documented policies may be counteracted by pro-active action at the level of the EC and compellingly, by the scientific dogma emanating through

the framework. It is also important to safeguard the objectivity of the entity co-ordinating the framework to mitigate any possible commandeering by the industry. This likelihood is lessened if funding is received directly from the EU budget with no financial support from the pharmaceutical companies. The model used for the European Centre for Disease Prevention and Control (ECDC) would be ideal for a public health agency co-ordinating the framework. The fact that the Member States come together and adopt a united and aligned approach also increases their strength when confronting the industry. Indirect and less visible influence on stakeholders (such as patient organisations) involved in decision-making at the level of the Access Framework should also be anticipated in light of similar experiences (Mandeville et al., 2019). Specific or conflicting interests must require mandatory disclosure in all circumstances and crucially, these should be managed through fully transparent modalities.

Appraisal of the Access Framework clearly highlights its value in generating data. It is imperative that this information, besides being fed back into the framework, is disseminated as broadly and relevantly as possible. This includes the regulatory system as well as operators in health care systems. The findings of this study, supported by the literature (Healy and Mangin, 2019), demonstrate that save for guidelines, pharmaceutical companies have gained control of information distribution channels. If effectively managed, data from the Access Framework could counterbalance this situation. The provision of information to health care professionals should not be left to the industry since it has huge impact on rational prescribing and use.

### 4.4.4 Application of the Access Framework

The commission, through its Pharmaceutical Strategy for Europe [65] aspires to ensure accessibility to affordable medicines as well as to bolster innovation of the European Industry. It does so mindful of ground-breaking scientific and commercial transformation but also cognisant of a daunting economic and social climate. Of the industry's ability to develop innovative therapies, there is little doubt. How affordable and accessible these will be is another matter. When asked to select therapies to pilot the Access Framework, focus group participants chose products which challenge even the most affluent and redoubtable of health systems. CAR T-Cell therapeutic agents were universally nominated by the group. These potent genetically-engineered immunotherapies have made possible a paradigm shift in cancer treatment.

As of May 2022, six such products have been authorised by the EMA (Jommi et al., 2022; Mikhael et al., 2022) with many more CAR therapies focusing on different approaches and malignancies expected to become available in the imminent future (Adami and Maher, 2021). The successes of the industry in their pursuit of innovative therapies render achieving access to affordable medicines across the EU much more onerous. Launch prices of CAR T-Cell treatments hover between €350,000 and €460,000 per course, whilst new chemotherapeutic and immunotherapeutic agents are expected to require anything from €650,000 to circa €1 million annually for each patient. These intimidating figures are as nothing when compared to those of another therapeutic group of agents selected by participants as a candidate for the

[65] European Commission. Communication from the Commission to the European Parliament, the Council. The European Economic and Social Committee and the Committee of the Regions [Internet]. Pharmaceutical Strategy for Europe. Brussels. 2020 [2023 Jan 5]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN]

Access Framework. The cost of gene therapies which give renewed hope to patients suffering from a diversity of disorders with limited alternative therapeutic options can climb up to €2.7 million per (1-time) treatment for each patient. Future novel personalised medicines will almost certainly present equal dilemmas in financial sustainability, not only in terms of direct expenses but also due to associated organisational and human resource requirements.

It is worth examining how the Access Framework could support CAR T-cell therapies since they were unanimously selected as the class of choice to pilot the framework. As can be expected, major hurdles would be faced in the uptake domain. These products are challenging to evaluate since they tend to be associated with a relatively high level of financial and clinical uncertainty, particularly when they have been placed on the market through a conditional marketing authorisation. Furthermore, their budgetary impact and sustainability is complex and goes beyond the cost of the product. The financial implications of personalised medicine spill over into the highly specialised resources necessary for CAR T-cell pre-treatment, administration and patient management at accredited medical centres. This includes the care required for dealing with potentially severe and less evidenced complications. The Access Framework can support capacity building in this regard, thus obtaining maximal value for investment. It can also encourage the "big sister" concept, twinning larger and smaller states to optimise resources. The relatively low patient numbers are a gating factor for the smaller states. These low volumes render building dedicated facilities economically unfeasible given the expertise and resources required. A better strategy would be pairing with another member state. The framework also provides the right opportunity to avoid valuable resource waste by supporting the alignment of regulatory and

HTA criteria, which are clear and consistent, and which should be included in future pre-approval study design requirements.

The weaker evidentiary base of CAR T-cell therapies renders post-entry data generation imperative, with the Access Framework being ideally suited for this purpose. Pooling Union-wide data requires a culture of quality assurance and disciplined self-reporting, which can be readily fostered through the framework. A major access issue would be explicit eligibility criteria for the judicious selection of candidate patients. This is important both from the perspective of equity, as well as to benchmark subsequent data evaluation and clinical outcome measurement. This should be complemented by guidance on accurate and harmonised efficacy and toxicity monitoring associated with long-term patient surveillance. In this context the Access Framework can link to the European Society for Blood and Marrow Transplantation (EBMT) registry, currently tracking post-authorisation safety surveillance (PASS) of these products to provide long-term outcome data.

Compatibility and interchange of information by regulators, health technology assessors, health system owners and other stakeholders may be facilitated through the framework. The framework can depend on strong scientific interaction across different disciplines and competences to better address still-evolving issues such as: demand and supply; inclusion/exclusion and remission criteria; possible modalities of optimising CAR T-cell persistency and potency; and determination of prospective health gains from one-off curative treatments. Academia can be mobilised to pursue conflict-free research such as unbiased economic analyses and clinical studies which include quality of life data. There is currently

reliance on industry-funded economic analysis. It is vital that independent critical review is carried out through data generated by the framework. The Access Framework also has the potential to identify more efficient organisational and technical methodologies, to lower costs and to determine improved reimbursement mechanisms by engaging with manufacturers, regulators, and payers. Open and ongoing dialogue with health service providers, experts and patient groups could also contribute to changes in health care models which may mitigate the high costs and logistical complexity associated with CAR T treatments.

Faced with a multitude of considerations that a new generation of advanced therapies brings, it is vital that we build a resilient and supportive framework that brings into focus the decisions that need to be taken and which offers best practice solutions. The great promise offered by advanced therapies is tempered by the challenges associated with their equitable accessibility to EU patients.

## 4.5 Limitations

Despite the wide spectrum of stakeholder perspectives represented in this study, two major actors have been excluded: patient representatives and the pharmaceutical industry. Both of these protagonists have a unique viewpoint which merits a specific research approach and focused study. It is also noteworthy that, whilst frequent reference is found in the literature regarding the opinions, experiences and concerns of the industry, the same cannot be said of patients. The prevailing methodology of patient engagement should be reviewed and revised to allow their voice to emerge clearly in active dialogue.

A heterogeneous group of protagonists from multiple disciplines across the EU were interviewed in this study. The objective of this research design was to obtain as broad an overview as possible. However, the weakness of this approach is that perceptions, although scientifically-based, may be conditioned by specific experiences of the local health care context. Where possible, follow-up interviews were held for more information and clarification to mitigate this issue. Moreover, a relatively larger proportion of Maltese participants contributed to this research. Throughout the study, this bias was mitigated as far as possible by differentiating the context of the Small States (including Malta) from that of the larger EU countries. Health care professionals in direct contact with patients were included in the initial part of this research generating important preliminary findings. This group included prescribers whose input incorporated the facet of information provision. It is clear from the findings that this aspect warrants more dedicated, in-depth study as to its relevance to ATM. Further work in this area has the potential to enhance and reinforce elements of the Access Framework.

This research was limited to an examination and evaluation of the post-entry domain of medicinal products in relation to ATM. It did not investigate how the medicines development model impacts on medicines' access. Neither did it explore the well-researched and the topics of medicines' trade laws, pricing, procurement and logistical availability, as associated with ATM.

Construct and content validation (i.e. whether a questionnaire measures what it is intended to measure, and whether a questionnaire covers all relevant aspects of the construct,

respectively) were not carried out since both questionnaires adopted in this study were exploratory in nature and not a final measure of ATM. These questionnaires, along with the unstructured interviews, were used as a preliminary tool to obtain the experiences and attitudes of healthcare professionals working closely with patients. The resultant data was evaluated in terms of its association to the research topic. These results were combined with those of the literature screening and used to formulate guides to the semi-structured interviews. However, since these semi-structured interviews were open-ended, the guide did not compromise the resultant data.

## 4.6 Recommendations for Future Research

This study has highlighted incongruencies between regulatory expectations and those of HTA. The wider health system is significantly impacted by regulatory decision-making. It is, therefore, justified to demand that the specifications of the regulatory approach should merge seamlessly with the HTA process and with clinical practice. Considerable work is required in this area with the objective of creating a single framework supporting the products' appropriate entry and use into the health system. This would facilitate and expedite reimbursement and pricing methodologies which are based on relevant outcomes. Defining such outcomes also necessitates further study enabling treatment benefit to be graded, including when outcomes are based on uncertain evidence, or when the benefit is marginal. Interesting work in this field has been initiated by the European Society for Medical Oncology (ESMO). The ESMO-Magnitude of Clinical Benefit Scale[66] has been developed

[66] ESMO. ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE. No Date [cited 2023 Jan 03]. Available from:

as a first step towards evidence-based decision-making in terms of the value of the therapy. Promoting accessibility and reducing access in equity are manifest objectives of this guide. More such tool kits should be developed and extended to other indications, ideally feeding back into the regulatory system.

Scientifically-based communication channels which are able to select and retrieve such data from the clinical setting and translate it back into the appropriate context should also be developed. It is essential that this includes the provision of impartial and complete information to clinicians and patients, particularly about new products and how they compare to alternative (or no) treatments. More specifically, this study demonstrated that there exists a need for an integrated communication structure which is fit for purpose. This structure should collate and disseminate comprehensive information to prescribers efficiently, and should have the capacity to proactively harness clinicians' experiences and input. Pragmatic solutions enabling patients to voice their concerns and to align treatment options which resonate with their preferences should also be identified and validated. Without equitable access to appropriate information, ATM cannot be effectively achieved and further work is necessary to examine and address this area.

Research exploring different models of drug development should also be undertaken, with the aim of enhanced alignment to public health needs. This represents an important component of access to appropriate medication. Health system needs should be overtly defined based on the current and expected burden of disease, and the pharmaceutical industry

https://www.esmo.org/content/download/288502/5736211/1/esmo-mcbs-booklet.pdf

should be proactively encouraged to develop products which target the identified gaps in the therapeutic armamentarium. Establishing priorities and incentivising the industry down these pathways, represents part of the solution to ATM. Studies should be carried out investigating how this may best be accomplished and examining how the Access Framework could contribute. The model adopted by the Drugs for Neglected Diseases initiative (DNDi)[67], which advocates for ATM and embraces sustainability principles, could be used as a basis for such research. Furthermore, different approaches of bringing drugs to market such as public-private collaboration, open-source research, and not-for-profit and public enterprise drug development ventures, should be examined for their feasibility and compatibility with the framework and their advantages to ATM.

The Access Framework developed through this research is essentially a tool-kit which fosters, evidences and optimises access to appropriate medication rationally prescribed and used. It should enable application to different therapeutic typologies, prompting systematic evaluation of the various applicable aspects of ATM. As part of their post-graduate training within their career path, pharmacists should be motivated to engage in such clinical reviews and audits, identifying possible areas and mechanisms of improving medicines' access. Above all, the Access Framework should be dynamic in nature, constantly evolving to meet new challenges and generate best-practice solutions. One such challenge comes in the form of the strategy towards greener medicines which the European Commission has embarked upon. This is intended to cover the entire life-cycle of pharmaceuticals from research and development, production, utilisation through to disposal. The impact that this may have on

[67] DNDI. Advocacy. Innovation and access to health technologies for all. No date [cited 2023 Jan 03]. Available from: https://dndi.org/advocacy/

ATM, and how these reverberations may be better managed through the framework, introduces an interesting new area of study.

## 4.7 Conclusion

Effective health care is largely contingent on ATM whose key aspects include that it should be timely and appropriate, providing evident value and benefit. Regrettably, patient Access to Medicines remains a challenge and a concern to many countries in Europe. This dilemma is compounded by a failure in equity, with European patients experiencing significant disparities to medicines' access, thus contributing to health inequalities across the Union. The vastly changing pharmaceutical landscape, whilst offering the possibility of profoundly-positive patient impact, simultaneously threatens to heighten these inequities. There is a need for greater solidarity in tackling health inequalities in the EU and broader and more concerted effort is necessary in this regard. The EC has highlighted this issue, placing it squarely on its agenda and emphasising the need for structures and methodologies which meaningfully support EU-wide access to essential and innovative therapies.

Over recent years the nature and pace of pharmaceutical advances has evolved significantly presenting the possibility of treating disorders that previously had no options. The scale of innovation has set a new bar in pharmaceutical care delivery and brought policy-makers under increasing pressure to approve and fund medicines which are hugely resource-demanding and whose assessment and appraisal may raise uncertainties. Against a backdrop of rising costs, increasing demand and finite resources, it is vital that the latter are used

optimally. The EC is justly determined to sustain this progress but it is important that the pivotal shift and accelerated growth of the industry is realised into actual patient benefit. It is also essential that this benefit is universally accessed by European patients and that access inequities are not heightened by these novel treatments. It is therefore critical that the science of, and capabilities in, the field of ATM, advances at a similar pace and calibre as the pharmaceutical innovation taking place.

The results of this study clearly establish the need for combined action at national and at EU level to achieve this aim. The findings highlight that access determinants are embedded and interconnected at different strata of the health system and action focusing on ATM should target all these levels. A lack, or an inadequacy, of policy prioritising medicines' access contributes to the problem. Informed policy-making is generally unrecognised and thus under-utilised as a tool for change and improvement, to strategically ameliorate ATM and mitigate barriers across the various stages of the products' life-cycle. Medicines policy should be based on defined public health goals and reasonable measures should be taken by the Member States to establish and operate an access policy which is fundamentally evidenced-based, which resonates with their health care model and which meets their health priorities. It should incorporate their long-term vision which has foresight of the innovative products in the pipeline and the step-change in health outcomes that they have the potential to deliver. The study results also demonstrate that regulatory legislation aiming to ensure appropriate standards of safety, quality and efficacy may have the undesired aftermath of reducing medicines' access, particularly in the smaller territories. Regulatory review and change should consider ATM as an additional objective to the currant parameters.

The study also identified several systemic weaknesses inherent in the European pharmaceutical infrastructure which negatively impact equitable ATM. There is currently a clear translational gap between outputs and public health needs and priorities and regulatory criteria must be revised to be more attuned to health care delivery requirements. It is proposed that the issues which fall short of ATM be addressed through a coherent and holistic pan-European structure. Through this research a conceptual framework incorporating key indicators within defined domains of the access pathway was presented, aiming to mitigate the challenges and tensions to ATM. Whilst contributing to the Access Framework, each territory may flexibly customise it to its unique model of health care delivery. This will not only support the Member States in achieving their national goals but also enable an increasingly harmonised pan-European approach to ATM.

The Access Framework, developed and validated through this study, creates an integrated evaluation cycle which fosters the collaborative generation of evidence to optimise the scientific quality of decision-making in this field. This should develop a quality and compliance status for ATM that meets the requirements of all stakeholders and focuses on what should be the priority in health care; the needs of patients.

The endeavour to improve appropriate and equitable medicines' access to patients in the EU, is a complex undertaking given the convoluted access pathway, the multiplicity of protagonists and the diversity of health care models and socio-economic elements involved. The Access Framework provides an effective platform to co-ordinate and guide joint action,

combining the expertise and efforts of the Member States in the direction of ATM. Meaningful progress and change depends on partnerships and networks collaborating to generate new levels of knowledge expansion and sharing. In turn, this should enable the formulation of agile, best-practice solutions and a policy blueprint for ongoing action supporting ATM. The Access Framework offers the potential to marshal science to prioritise medicines' access and deliver tangible outcomes that bring benefit to patients.

# References

Abimbola S, Topp SM. Adaptation with robustness: The case for clarity on the use of "resilience" in health systems and global health. BMJ Glob Heal 2018;3:1–4. https://doi.org/10.1136/bmjgh-2018-000758.

Abraham J. Partial progress: Governing the pharmaceutical industry and the NHS, 1948-2008. J Health Polit Policy Law 2009;34:931–77. https://doi.org/10.1215/03616878-2009-032.

Abraham J. The science and politics of medicines control. Drug Saf 2003;26:135–43. https://doi.org/10.4324/9780203056639.

Abraham J, Reed T. Progress , Innovation and Regulatory Science in Drug Development : The Politics of Intrnational Standard-Stting. Soc Stud Sci 2002;32:337–69.

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason JE, et al. Two-Year Follow-up of Transcend NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (liso-cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphomas (LBCL). Blood 2021;138:2840–2840. https://doi.org/10.1182/blood-2021-148948.

Acosta A, Ciapponi A, Aaserud M, Vietto V, Austvoll-Dahlgren A, Kösters JP, et al. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database Syst Rev 2014;10. https://doi.org/10.1002/14651858.CD005979.pub2.www.cochranelibrary.com.

Adami A, Maher J. An overview of CAR T-cell clinical trial activity to 2021. Immunother Adv 2021;1:1–3. https://doi.org/10.1093/immadv/ltab004.

Afzali M, Khorasani E, Alvandi M, Sabbagh-Bani-Azad M, Sharif Z, Saiyarsarai P, et al. Providing a framework for assessment of the access to medicine. DARU, J Pharm Sci 2019;27:243–54. https://doi.org/10.1007/s40199-019-00268-1.

Agomo CO, Ogunleye J, Portlock J. A survey to identify barriers in the public health role of community pharmacists. J Pharm Health Serv Res. 2016;7(4):253–261.

Allin S, Grignon M, Le Grand J. Subjective unmet need and utilization of health care services in Canada: What are the equity implications? Soc Sci Med 2010;70:465–72. https://doi.org/10.1016/j.socscimed.2009.10.027.

Almarsdóttir AB, Kaae S, Traulsen JM. Opportunities and challenges in social pharmacy and pharmacy practice research. Res Social Adm Pharm 2014;10:252–5. https://doi.org/10.1016/j.sapharm.2013.04.002.

Angelis A, Linch M, Montibeller G, Molina-Lopez T, Zawada A, Orzel K, et al. Multiple Criteria Decision Analysis for HTA across four EU Member States: Piloting the Advance Value Framework. Soc Sci Med 2020;246:112595. https://doi.org/10.1016/j.socscimed.2019.112595.

Appleby J, Helderman JK, Gregory S. The global financial crisis, health and health care. Heal Econ Policy Law 2015;10:1–6. https://doi.org/10.1017/S1744133114000206.

Asad AI, Popesko B. Contemporary challenges in the European pharmaceutical industry: a systematic literature review. Meas Bus Excell 2022. https://doi.org/10.1108/MBE-09-2021- 0112.

Asadi-Lari M, Packham C, Gray D. Need for redefining needs. Health Qual Life Outcomes 2003;1:1–5. https://doi.org/10.1186/1477-7525-1-34.

Assarroudi A, Heshmati Nabavi F, Armat MR, Ebadi A, Vaismoradi M. Directed qualitative content analysis: the description and elaboration of its underpinning methods and data analysis process. J Res Nurs 2018;23:42–55. https://doi.org/10.1177/1744987117741667.

Axelsson MAB, Spetz M, Mellén A, Wallerstedt SM. Use of and attitudes towards the prescribing guidelines booklet in primary health care doctors. BMC Clin Pharmacol 2008;8:1–8. https://doi.org/10.1186/1472-6904-8-8.

Azzopardi-Muscat N, Sorensen K, Aluttis C, Pace R, Brand H. Europeanisation of health systems: A qualitative study of domestic actors in a small state. BMC Public Health 2016;16:1–15. https://doi.org/10.1186/s12889-016-2909-0.

Babar ZUD, Gammie T, Seyfoddin A, Hasan SS, Curley LE. Patient access to medicines in two countries with similar health systems and differing medicines policies: Implications from a comprehensive literature review. Res Soc Adm Pharm 2019;15:231–43. https://doi.org/10.1016/j.sapharm.2018.04.006.

Baker DE. High Drug Prices: So Who Is to Blame? Hosp Pharm 2017;52:5–6. https://doi.org/10.1310/hpj5201-5.

Balasegaram M, Bréchot C, Farrar J, Heymann D, Ganguly N, Khor M, et al. A Global Biomedical R&D Fund and Mechanism for Innovations of Public Health Importance. PLoS Med 2015;12:1–5. https://doi.org/10.1371/journal.pmed.1001831.

Barei F. Value-added medicines: is there any room between market access challenges and "patient centricity"? Int J Pharm Healthc Mark 2018;12:71–6. https://doi.org/10.1108/IJPHM-11-2016-0058.

Barlow JF, Yang M, Teagarden JR. Are Payers Ready, Willing, and Able to Provide Access to New Durable Gene Therapies? Value Heal 2019;22:642–7. https://doi.org/10.1016/j.jval.2018.12.004.

Bayntun C. A health system approach to all-hazards disaster management: A systematic review. PLoS Curr 2012. https://doi.org/10.1371/50081cad5861d.

Beatty PC, Willis GB. Research synthesis: The practice of cognitive interviewing. Public Opin Q 2007;71:287–311. https://doi.org/10.1093/poq/nfm006.

Beaussier AL, Cabane L. Strengthening the EU's response capacity to health emergencies: Insights from eu crisis management mechanisms. Eur J Risk Regul 2020;11:808–20. https://doi.org/10.1017/err.2020.80.

Belloni A, Morgan D, Paris V. Pharmaceutical Expenditure And Policies : Past Trends And Future Challenges. OECD Heal Work Pap 2016:0–75.

Bertinato L, Busse R, Fahy N, Legido-Quigley H, Mckee M, Palm W, et al. Policy Brief: Cross-Border Health Care in Europe. World Heal Organ Behalf Eur Obs Heal Syst Policies 2005.

Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B, et al. Access to medicines from a health system perspective. Health Policy Plan 2013a;28:692–704. https://doi.org/10.1093/heapol/czs108.

Bigdeli M, Javadi D, Hoebert J, Laing R, Ranson K, Arhinful D, et al. Health policy and systems research in access to medicines: A prioritized agenda for low- and middle-income countries. Heal Res Policy Syst 2013b;11:1–13. https://doi.org/10.1186/1478-4505-11-37.

Bigdeli M, Rouffy B, Lane BD, Schmets G, Soucat A. Health systems governance: The missing links. BMJ Glob Heal 2020;5:1–6. https://doi.org/10.1136/bmjgh-2020-002533.

Bigdeli M, Shroff ZC, Godin I, Ghaffar A. Health systems research on access to medicines: Unpacking challenges in implementing policies in the face of the epidemiological transition. BMJ Glob Heal 2018;2:1–4. https://doi.org/10.1136/bmjgh-2018-000941.

Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med 2022;386:629–39. https://doi.org/10.1056/nejmoa2116596.

Bond K, Stiffell R, Ollendorf DA. Principles for deliberative processes in health technology assessment. Int J Technol Assess Health Care 2020;36:445–52. https://doi.org/10.1017/S0266462320000550.

Börzel TA. Member State Responses to Europeanization. JCMS J Common Mark Stud 2002;40:193–214. https://doi.org/10.1111/1468-5965.00351.

Borzell TA, Risse T. When Europe Hits Home: Europeanization and Domestic Change. EUI Working Papers. RSC No. 2000/56. Eur Univ Inst 2000.

Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One 2011;6:1–10. https://doi.org/10.1371/journal.pone.0020476.

Briguglio L. Introduction: Small states and the European Union. In: Briguglio L, editor. Small States and the European Union. Economic Perspectives. 1st ed. New York: Routledge; 2016. p. 1-45.

Bryman A. Social Research Methods. 4th ed. Oxford: Oxford University Press; 2001.

Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. Nat Rev Drug Discov 2021;20:254–5. https://doi.org/10.1038/d41573-021-00037-3.

Burci GL, Gostin LO. Privatized pharmaceutical innovation vs access to essential medicines: A global framework for equitable sharing of benefits. JAMA - J Am Med Assoc 2017;317:473–4. https://doi.org/10.1001/jama.2016.17994.

Burke S, Parker S, Fleming P, Barry S, Thomas S. Building health system resilience through policy development in response to COVID-19 in Ireland: From shock to reform. Lancet Reg Heal - Eur 2021;9:100223. https://doi.org/10.1016/j.lanepe.2021.100223.

Burris S, Wagenaar AC, Swanson J, Ibrahim JK, Wood J, Mello MM. Making the case for laws that improve health: A framework for public health law research. Milbank Q 2010;88:169–210. https://doi.org/10.1111/j.1468-0009.2010.00595.x.

Büssgen M, Stargardt T. Changes in launch delay and availability of pharmaceuticals in 30 European markets over the past two decades. BMC Health Serv Res 2022;22:1–11. https://doi.org/10.1186/s12913-022-08866-7.

Califf RM, Slavitt A. Lowering Cost and Increasing Access to Drugs Without Jeopardizing Innovation. JAMA - J Am Med Assoc 2019;321:1571–3. https://doi.org/10.1001/jama.2019.3846.

Campbell SM, Roland MO, Buetow SA. Defining quality of care. Soc Sci Med 2000;51:1611–25. https://doi.org/10.1016/S0277-9536(00)00057-5.

Capkun G, Corry S, Facey K. Can we use existing guidance to support the development of robust real-world evidence for health technology assessment / payer. Int J Technol Assess Health Care 2022;38.

Caporaso J. The three worlds of regional integration theory. In: Graziano P, Vink MP, editors. Europeanization New Research Agendas. 1st ed. London: Paul Grave Macmillan; 2008. p 23-34.

Carey MA, Asbury J-E. Focus group research. Ebook Edit. New York: Taylor and Francis Group; 2012. https://doi.org/10.4324/9781315428376.

Carone G, Schwierz C, Xavier A, Commission E, General D, Affairs F. European Economy. Cost-containment policies in public pharmaceutical spending in the EU. European Commission; 2012. https://doi.org/10.2765/27111.

Cavaleri M, Sweeney F, Gonzalez-Quevedo R, Carr M. Shaping EU medicines regulation in the post COVID-19 era. Lancet Reg Heal - Eur 2021;9:100192. https://doi.org/10.1016/j.lanepe.2021.100192.

Cavalieri M. Geographical variation of unmet medical needs in Italy: A multivariate logistic regression analysis. Int J Health Geogr 2013;12:1. https://doi.org/10.1186/1476-072X-12-27.

Charles O, Onakpoya I, Benipal S, Id HW, Id AB. Withdrawn medicines included in the essential medicines lists of 136 countries. LOS ONE 2019;14:1–13. https://doi.org/10.1371/journal.pone.0225429.

Chaupain-Guillot S, Guillot O. Health system characteristics and unmet care needs in Europe: an analysis based on EU-SILC data. Eur J Heal Econ 2015;16:781–96. https://doi.org/10.1007/s10198-014-0629-x.

Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol 2016;27:1423–43. https://doi.org/10.1093/annonc/mdw213.

Ciani O, Grigore B, Blommestein H, de Groot S, Möllenkamp M, Rabbe S, et al. Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies. Med Decis Mak 2021;41:439–52. https://doi.org/10.1177/0272989X21994553.

Clarke D, Rajan D, Schmets G. Creating a supportive legal environment for universal health coverage. Bull World Health Organ 2016;94:482. https://doi.org/10.2471/BLT.16.173591.

Colbert A, Rintoul A, Simão M, Hill S, Swaminathan S. Can affordability and innovation coexist for medicines? BMJ 2020;368:115. https://doi.org/10.1136/bmj.l7058.

Conti RM, Rosenthal MB. Pharmaceutical Policy Reform — Balancing Affordability. N Engl J Med 2016;344. https://doi.org/10.1056/NEJMp1600233.

Costa-Font J, Kanavos P, Rovira J. Determinants of out-of-pocket pharmaceutical expenditure and access to drugs in Catalonia. Appl Econ 2007;39:541–51. https://doi.org/10.1080/00036840500438947.

Costa-Font J, McGuire A, Varol N. Regulation effects on the adoption of new medicines. Empir Econ 2015;49:1101–21. https://doi.org/10.1007/s00181-014-0903-x.

Cox JL, Gerard DP. Achieving access : addressing the needs of payors and health technology assessment agencies. Eur Hear J Suppl 2015;17:15–20. https://doi.org/10.1093/eurheartj/suv041.

Créange A, Careyron A. The diagnosis of chronic inflammatory demyelinating polyneuropathy: a Delphi-method approach. J Neurol 2013;260:3015–22. https://doi.org/10.1007/s00415-013-7100-2.

Crouch M, McKenzie H. The logic of small samples in interview-based qualitative research. Soc Sci Inf 2006;45:483–99. https://doi.org/10.1177/0539018406069584.

Culyer AJ, Lomas J. Deliberative processes and evidence-informed decision making in healthcare: Do they work and how might we know? Evid Policy 2006;2:357–71. https://doi.org/10.1332/174426406778023658.

Cummings JR, Wen H, Ko M, Druss BG. Race/ethnicity and geographic access to medicaid substance use disorder treatment facilities in the United States. JAMA Psychiatry 2014;71:190–6. https://doi.org/10.1001/jamapsychiatry.2013.3575.

Dalton K, Connery C, Murphy KD, O'Neill D. Pharmacists' views on the impact of the Falsified Medicines Directive on community pharmacies: A cross-sectional survey. Explor Res Clin Soc Pharm 2022;5:100127. https://doi.org/10.1016/j.rcsop.2022.100127.

Danzon PM, Epstein AJ. Effects of regulation on drug launch and pricing in interdependent markets. vol. 23. Emerald Group Publishing Ltd.; 2012. https://doi.org/10.1108/S0731-2199(2012)0000023005.

Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs - Evidence from twenty-five major markets in the 1990s. Health Econ 2005;14:269–92. https://doi.org/10.1002/hec.931.

Davidová J, Ivanovic N, Práznovcová L. Participation in pharmaceutical costs and seniors' access to medicines in the Czech Republic. Cent Eur J Public Health 2008;16:26–8. https://doi.org/10.21101/cejph.a3439.

Davis C, Abraham J. Unhealthy Pharmaceutical Regulation. Palgrave Macmillan; 2013. https://doi.org/10.1057/9781137349477.

Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency : retrospective cohort study of drug approvals 2009-13. BMJ 2017;359. https://doi.org/10.1136/bmj.j4530.

Dawson C. Introduction to Research Methods 5th Edition: A Practical Guide for Anyone Undertaking a Research Project. 4th ed. Oxford: How To Content; 2012.

DeJonckheere M, Vaughn LM. Semistructured interviewing in primary care research: a balance of relationship and rigour. BMJ. 2016;7(57):1-8.

Denzin NK, Lincoln YS. The SAGE Handbook of Qualitative Research | SAGE Publications Ltd. 4th ed. London: Sage; 2010.

Detiček A, Locatelli I, Kos M. Patient Access to Medicines for Rare Diseases in European Countries. Value Heal 2018;21:553–60. https://doi.org/10.1016/j.jval.2018.01.007.

DiCicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ 2006;40:314–21. https://doi.org/10.1111/j.1365-2929.2006.02418.x.

Donyai P. Pharmacy practice research methods: An Overview. Springer International Publishing; 2015.

Dsc RA, Murphy LA, Solà-morales O, Cunningham D, Mestre-ferrandiz J, Pouvourville G De. Using Real-World Data in the Health Technology Assessment of Pharmaceuticals: Strengths, Difficulties, and a Pragmatic Way Forward. Value Heal 2023;26:11–9. https://doi.org/10.1016/j.jval.2023.01.010.

Duong M, Moles RJ, Chaar B, Chen TF. Essential medicines in a high income country: Essential to whom? PLoS One 2015;10:1–15. https://doi.org/10.1371/journal.pone.0143654.

Dyson K. Introduction: EMU as Integration, Europeanization, and Convergence. In: Dyson K, editor. European States and the Euro: Europeanization, Variation, and Convergence. 1st ed. Oxford: Oxford University Press; 2002. p 1-28.

Dyson K, Goetz KH. Living with Europe: Power, Constraint, and Contestation. Ger Eur Polit Constraint 2012. https://doi.org/10.5871/bacad/9780197262955.003.0001.

Eichler HG, Cavaleri M, Enzmann H, Scotti F, Sepodes B, Sweeney F, et al. Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity? Clin Pharmacol Ther 2020;108:730–3. https://doi.org/10.1002/cpt.1891.

Eichler HG, Pignatti F, Schwarzer-Daum B, Hidalgo-Simon A, Eichler I, Arlett P, et al. Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. Clin Pharmacol Ther 2021;109:1212–8. https://doi.org/10.1002/cpt.2083.

Elliott T, Tyrer P, Horwood J, Fergusson D. Assessment of abnormal personality in childhood: a Delphi survey of questionnaire data. J Pers Disord 2011;25:89–100. https://doi.org/10.1521/pedi.2011.25.1.89.

Ernst M, Oeser A, Besiroglu B, M AEA, Monsef I, Borchmann P, et al. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory di use large B-cell lymphoma. Cochrane Database Syst Rev 2021. https://doi.org/10.1002/14651858.CD013365.pub2.www.cochranelibrary.com.

European Federation of Pharmaceutical Industries and Associations. Addressing Patient Access Inequalities in Europe 2022.

Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: Systematic review and mta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trails. BMJ 2010. https://doi.org/10.2307/25738448.

Facey KM, Rannanheimo P, Batchelor L, Borchardt M, De Cock J. Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU - Actions for stakeholders. Int J Technol Assess Health Care 2020;36:459–68. https://doi.org/10.1017/S026646232000063X.

Featherstone K, Kazamias G. Southern Europe and the process of “Europeanization.” South Eur Soc Polit 2000;5:1–24. https://doi.org/10.1080/13608740508539600.

Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med 2015;124:39–47. https://doi.org/10.1016/j.socscimed.2014.11.003.

Fink A. How to Conduct Surveys A Step-by-Step Guide. 4th ed. Los Angeles: Sage; 2009.

Fiorillo D. Reasons for unmet needs for health care: the role of social capital and social support in some western EU countries. Int J Heal Econ Manag 2020;20:79–98. https://doi.org/10.1007/s10754-019-09271-0.

Fittler A, Richter K, Vajda P, Bodrogi Z, Vida R, Bella R, et al. 2SPD-023 How much does falsified medicines directive actually costs? Detailed cost evaluation of serialisation in a representative sample of Hungarian hospital pharmacies 2020:A19.2-A20. https://doi.org/10.1136/ejhpharm-2020-eahpconf.42.

Fjaer EL, Stornes P, Borisova L V., McNamara CL, Eikemo TA. Subjective perceptions of unmet need for health care in Europe among social groups: Findings from the European social survey (2014) special module on the social determinants of health. Eur J Public Health 2017;27:82–9. https://doi.org/10.1093/eurpub/ckw219.

Flick U. An Introduction to Qualitative Research. 4th ed. London: Sage; 2009.

Flockhart T. Europeanization or EU-ization? The Transfer of European Norms across Time and Space. J Common Mark Stud 2010;48:787–810. https://doi.org/10.1111/j.1468-5965.2010.02074.x.

Flume M, Bardou M, Capri S, Sola-morales O, Cunningham D, Levin L-A, et al. Approaches to manage “affordability” of high budget impact medicines in key EU countries. J Mark Access Heal Policy 2018;6. https://doi.org/10.1080/20016689.2018.1478539.

Forman, L. “rights” and wrongs: what utility for the right to health in reforming trade rules on medicines? Health and Human Rights. 2008;10(2):37-52

Fridell M, Edwin S, Schreeb J von, Saulnier DD. Health system resilience: what are we talking about? A scoping review mapping characteristics and keywords. Int J Heal Policy Manag 2020;9:6–16. https://doi.org/10.15171/ijhpm.2019.71.

Gambardella A, Orsenigo L, Pammolli F. Global Competitiveness in Pharmaceuticals: A European Perspective. Munich Pers RePEc Arch 2000.

Garrison L, Towse A. The Drug Budget Silo Mentality in Europe: An Overview. Value Heal 2003;6:S1–9. https://doi.org/10.1046/j.1524-4733.6.s1.8.x.

Goldacre B. Bad pharma: How medicine is broken, and how we can fix it. London: Fourth Estate; 2012.

Green J. The Use of Focus Groups in Research into Health. In: Saks M, Allsop J, editors. Researching Health: Qualitative, Quantitative and Mixed Methods. 1st ed. London: Sage Publications; 2007. p. 112-132.

Greenbaum TL. The Handbook for Focus Group Research. 2nd ed. California: Sage Publications; 1998. https://doi.org/10.4135/9781412986151. Gribben J, Chabannon C, Yakoub-agha I, Einsele H. The EBMT/EHA CAR-T Cell Handbook. 2022. https://doi.org/10.1007/978-3-030-94353-0.

Gunn SWA, Masellis M. The Declaration of Alma-Ata. Int Conf Prim Heal Care 1978:21–3. https://doi.org/10.1007/978-0-387-72264-1_4.

Guthmuller S, Paruolo P, Verzillo S. Positive externalities of eu actions on sustainability of health systems. Sustain Heal Care Syst Eur Contrib to Econ Anal 2021;295:1–21. https://doi.org/10.1108/S0573-855520210000295006.

Hagaman AK, Wutich A. How Many Interviews Are Enough to Identify Metathemes in Multisited and Cross-cultural Research? Another Perspective on Guest, Bunce, and Johnson's (2006) Landmark Study. Field Methods 2017;29:23–41. https://doi.org/10.1177/1525822X16640447.

Hanson WE, Creswell JW, Clark VLP, Petska KS, Creswell JD. Mixed methods research designs in counseling psychology. J Couns Psychol 2005;52:224–35. https://doi.org/10.1037/0022-0167.52.2.224.

Harrison J, Young J, Butow P, Solomon M. Needs in Health Care: What Beast is That? Int J Heal Serv 2013;43:567–85. https://doi.org/10.2190/HS.43.3.l.

Hasan SS, Lu CY, Babar ZUD. Access to High Cost Medicines: An Overview. Equitable Access to High-Cost Pharm 2018:1–10. https://doi.org/10.1016/B978-0-12-811945-7.00001-4.

Hasenclever L, Miranda C, Chaves G, Peixoto ALA, Mattos LV, Viana J de S. Controversial aspects of the concept of health needs and their impact on the accessibility of medicine and health services. Cienc e Saude Coletiva 2021;26:5401–10. https://doi.org/10.1590/1413-812320212611.44362020.

Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008–15.

Hawksbee L, McKee M, King L. Don't worry about the drug industry's profits when considering a waiver on covid-19 intellectual property rights. BMJ 2022;376:67367. https://doi.org/10.1136/bmj.o482.

Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. Br Med J 1999;319:652–3. https://doi.org/10.1136/bmj.319.7211.652.

Heads of Medicines Agencies. EU Medicines Agencies Network Strategy to 2020 - Working together to improve health. Eur Med Agency 2015:1–26.

Healy D, Mangin D. Clinical judgments, not algorithms, are key to patient safety - An essay by David Healy and Dee Mangin. BMJ 2019;367. https://doi.org/10.1136/bmj.l5777.

Henshall C, Mardhani-Bayne L, Frønsdal KB, Klemp M. Interactions between health technology assessment, coverage, and regulatory processes: Emerging issues, goals, and opportunities. Int J Technol Assess Health Care 2011;27:253–60. https://doi.org/10.1017/S0266462311000262.

Hoebert JM, van Dijk L, Mantel-Teeuwisse AK, Leufkens HGM, Laing RO. National medicines policies - a review of the evolution and development processes. J Pharm Policy Pract 2013;6:1–10. https://doi.org/10.1186/2052-3211-6-5.

Hogerzeil H V. Essential medicines and human rights: What can they learn from each other? Bull World Health Organ 2006;84:371–5. https://doi.org/10.2471/BLT.06.031153.

Hogerzeil H V, Samson M, Casanovas JV, Rahmani-Ocora L. Is access to essential medicines as part of the fulfilment of the right to health enforceable through the courts? Lancet 2006;368:305–11. https://doi.org/10.1016/S0140-6736(06)69076-4.

Holzhacker R, Haverland M. European research reloaded: Cooperation and integration among europeanized states. Eur Res Reloaded Coop Integr among Eur States 2006:1–273. https://doi.org/10.1007/1-4020-4430-5.

Holzinger K, Schimmelfennig F. Differentiated integration in the european union: Many concepts, sparse theory, few data. J Eur Public Policy 2012;19:292–305. https://doi.org/10.1080/13501763.2012.641747.

Howell K. Developng Conceptualizations of Europeanization and European Integration: Mixing Methodologies. Group 2002:1–27.

Howell KE. Developing Conceptualisations of Europeanisation: A Study of Financial Services. Politics 2004;24:20–5. https://doi.org/10.1111/j.1467-9256.2004.00201.x.

Hsieh H-F, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15:1277–88. https://doi.org/10.1177/1049732305276687.

Husereau D, Reed SD. A Beginner's Guide to Understanding Curative Therapies. Value Heal 2019;22:619–20. https://doi.org/10.1016/j.jval.2019.04.1910.

Hutton J, Trueman P, Facey K. Harmonization of evidence requirements for health technology assessment in reimbursement decision making. Int J Technol Assess Health Care 2008;24:511–7. https://doi.org/10.1017/S0266462308080677.

Hwang TJ, Kesselheim AS, Vokinger KN. Reforming the World Health Organization's Essential Medicines List. Essential but Unaffordable. JAMA 2022;328:1807–8. https://doi.org/10.1093/annonc/mdx310.

Hwang TJ, Ross JS, Vokinger KN, Kesselheim AS. Association between FDA and EMA expedited approval programs and therapeutic value of new medicines: Retrospective cohort study. BMJ 2020;371:1–8. https://doi.org/10.1136/bmj.m3434.

Jacobson C, Locke FL, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-Term (≥4 Year and ≥5 Year) Overall Survival (OS) By 12- and 24-Month Event-Free Survival (EFS): An Updated Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma (LBCL). Blood 2021;138:1764–1764. https://doi.org/10.1182/blood-2021-148078.

Jiang M, Yang S, Yan K, Liu J, Zhao J, Fang Y. Measuring Access to Medicines: A Survey of Prices, Availability and Affordability in Shaanxi Province of China. PLoS One 2013;8:1–8. https://doi.org/10.1371/journal.pone.0070836.

Jommi C, Bramanti S, Pani M, Ghirardini A, Santoro A. CAR T-Cell Therapies in Italy: Patient Access Barriers and Recommendations for Health System Solutions. Front Pharmacol 2022;13:1–11. https://doi.org/10.3389/fphar.2022.915342.

Jonathan N, Shimshon B. Pharmaceuticals: Beating the Hell Out of the Average Pharmaceuticals : Beating the Hell Out of the Average, Research Note, The Bichler and Nitzan Archivs 2021.

Jongh TDE, Velten L, Schrijver L. Access to medicinal products. Study for the Committee on Environment, Public Health and Food Safet. Policy Dep Econ Sci Qual Life, Eur Parliam Luxemb 2021:1–114.

Jönsson B, Hofmarcher T, Lindgren P, Wilking N. Comparator report on patient access to cancer medicines in Europe revisited. IHE Report 2016:4, IHE:Lund.

Kaae S, Traulsen JM. Quality Methods in Pharmacy Practice Research. Switzerland: Springer; 2015. https://doi.org/10.1007/978-3-319-14672-0.

Kamdar M, Solomon SR, E. AJ, Johnston PB, Glass B, Bachanova V. Lisocabtagene Maraleucel (liso-cel), a CD19-Directed Chimeric Antigen Receptor (CAR) T Cell Therapy, Versus Standard of Care (SOC) with Salvage Chemotherapy (CT) Followed By Autologous

Stem Cell Transplantation (ASCT) As Second-Line (2L) Treatment in Pati. Blood 2021;138:91–4. https://doi.org/10.1182/blood-2021-147913.

Kanavos P. Overview of Pharmaceutical Pricing and Reimbursement Regulation in Europe. Japanese Pharmacol Ther 2003;31:819–36.

Kandolf Sekulovic L, Peris K, Hauschild A, Stratigos A, Grob JJ, Nathan P, et al. More than 5000 patients with metastatic melanoma in Europe per year do not have access to recommended first-line innovative treatments. Eur J Cancer 2017;75:313–22. https://doi.org/10.1016/j.ejca.2017.01.012.

Kar SS, Pradhan HS, Mohanta GP. Concept of essential medicines and rational use in public health. Indian J Community Med 2010;35:10–3. https://doi.org/10.4103/0970- 0218.62546.

Kazakov R. Pricing and reimbursement policies in new EU accession countries. J Generic Med 2007;4:249–58. https://doi.org/10.1057/palgrave.jgm.4950068.

Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. Int J Nurs Stud 2001;38:195–200. https://doi.org/10.1016/s0020- 7489(00)00044-4.

Kennedy D. Drug prices: Real problem, wrong solution. Science (80- ) 2001;292:1797. https://doi.org/10.1126/science.292.5523.1797.

Kim H, Goodall S, Liew D. Health Technology Assessment Challenges in Oncology: 20 Years of Value in Health. Value Heal 2019;22:593–600. https://doi.org/10.1016/j.jval.2019.01.001.

Konijn P. Pharmaceutical Products - comparitive price levels in 33 European countries in 2005. Econ Financ 2007;45:2005–8.

Krikorian G, Torreele E. We Cannot Win the Access to Medicines Struggle Using the Same Thinking That Causes the Chronic Access Crisis. Heal Hum Rights J 2021;23:119–27.

Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Glob Heal 2018;6:e1196–252. https://doi.org/10.1016/S2214-109X(18)30386-3.

Kruk ME, Myers M, Varpilah ST, Dahn BT. What is a resilient health system? Lessons from Ebola. Lancet 2015;385:1910–2. https://doi.org/10.1016/S0140-6736(15)60755-3.

Kuipers E, Wensing M, De Smet PAGM, Teichert M. Barriers and facilitators for community pharmacists' participation in pharmacy practice research: a survey. Int J Pharm Pract. 2019;27(4):399-402.

Kvale S. InterViews: An Introduction to Qualitative Research Interviewing. London: 1996. https://doi.org/10.1016/S1098-2140(99)80208-2.

Ledley FD, McCoy SS, Vaughan G, Cleary EG. Profitability of Large Pharmaceutical Companies Compared with Other Large Public Companies. JAMA - J Am Med Assoc 2020;323:834–43. https://doi.org/10.1001/jama.2020.0442.

Leung F-H, Savithiri R. Spotlight on focus groups. Can Fam Physician 2009;55:218–9.

Lindee S, Abraham J. Science, Politics, and the Pharmaceutical Industry: Controversy and Bias in Drug Regulation. Technol Cult 1998;39:336. https://doi.org/10.2307/3107068.

Linstone HA, Turoff M. Introduction. In: Linstone HA, Turoff M, editors. The Delphi Method Techniques and Applications. 1st ed. Boston: Addison-Wesley Pub. Co. 2002. p 3-12.

Lloyd-Williams H, Hughes DA. A systematic review of economic evaluations of advanced therapy medicinal products. Br J Clin Pharmacol 2021;87:2428–43. https://doi.org/10.1111/bcp.14275.

Locke FL, Miklos DB, Jacobson CA, Perales M-A, Kersten M-J, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med 2022;386:640–54. https://doi.org/10.1056/nejmoa2116133.

Loder E, Godlee F. Missing clinical trial data: Setting the record straight. BMJ 2010;341:787–8. https://doi.org/10.1136/bmj.c5641.

Low J. Unstructured Interviews and Health Research. In: Saks M, Allsop J, editors. Researching Health: Qualitative, Quantitative and Mixed Methods. 1st ed. London: Sage Publications; 2007. p. 74-91.

Malterud K. Qualitative research: standards, challenges, and guidelines. Lancet (London, England) 2001;358:483–8. https://doi.org/10.1016/S0140-6736(01)05627-6.

Mandeville KL, Barker R, Packham A, Sowerby C, Yarrow K, Patrick H. Financial interests of patient organisations contributing to technology assessment at England's National Institute for Health and Care Excellence: Policy review. BMJ 2019;364. https://doi.org/10.1136/bmj.k5300.

Manikandan S. Are we moving towards a new definition of essential medicines? J Pharmacol Pharmacother 2015;6:123–5. https://doi.org/10.4103/0976-500X.162008.

Martinalbo J, Bowen D, Camarero J, Chapelin M, Démolis P, Foggi P, et al. Early market access of cancer drugs in the EU. Ann Oncol 2016;27:96–105. https://doi.org/10.1093/annonc/mdv506.

Maynard A, Cookson R. Money or your life? The health-wealth trade-off in pharmaceutical regulation. J Heal Serv Res Policy 2001;6:186–9. https://doi.org/10.1258/1355819011927341.

McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm 2016;38:655–62. https://doi.org/10.1007/s11096-016-0257-x.

Merks P, Religioni U, de Castro NP, Augustynowicz A, Plagens-Rotman K, Brindley D, et al. Falsified Medicines Directive in a Secondary Care Environment—Impact on Supply Chain. Int J Environ Res Public Health 2022;19. https://doi.org/10.3390/ijerph19063276.

Michalopoulos S. Pharma Industry Cannot Escape Drug Price Talks. Brussels: 2016.
Mikhael J, Fowler J, Shah N. Chimeric Antigen Receptor T-Cell Therapies: Barriers and Solutions to Access. JCO Oncol Pract 2022;18:800–7. https://doi.org/10.1200/op.22.00315.

Mills M, Kanavos P. Do pharmaceutical budgets deliver financial sustainability in healthcare? Evidence from Europe. Health Policy (New York) 2020;124:239–51. https://doi.org/10.1016/j.healthpol.2019.12.002.

Mintzes B, Vitry A. Flawed evidence underpins approval of new cancer drugs. BMJ 2019;366. https://doi.org/10.1136/bmj.l5399.

Moberly T. NHS joint working with industry is out of public sight. BMJ 2019;364. https://doi.org/10.1136/bmj.l1353.

Moermond CTA, Puhlmann N, Brown AR, Owen SF, Ryan J, Snape J, et al. GREENER Pharmaceuticals for More Sustainable Healthcare. Environ Sci Technol Lett 2022;9:699–705. https://doi.org/10.1021/acs.estlett.2c00446.

Moloney R, Mohr P, Hawe E, Shah K, Garau M, Towse A. PAYER PERSPECTIVES on FUTURE ACCEPTABILITY of COMPARATIVE EFFECTIVENESS and RELATIVE EFFECTIVENESS RESEARCH. Int J Technol Assess Health Care 2015;31:90–8. https://doi.org/10.1017/S0266462315000203.

Morgan S, McMahon M, Greyson D. Balancing health and industrial policy objectives in the pharmaceutical sector: Lessons from Australia. Health Policy (New York) 2008;87:133–45. https://doi.org/10.1016/j.healthpol.2008.01.003.

Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. BMJ 2020;368:1–4. https://doi.org/10.1136/bmj.l4627.

Mossialos E, McKee M. Is a European healthcare policy emerging? BMJ 2001;323:248–248. https://doi.org/10.1136/bmj.323.7307.248.

Mossialos E, Mrazek M, Walley T. Regulating pharmaceuticals in Europe : striving for efficiency , equity and quality. Maidenhead UK: Open University Press; 2004.

Mossialos E, Permanand G, Baeten R, Hervey TK. Health Systems Governance in Europe: The Role of EU Law and Policy. Cambridge University Press, Cambridge, UK; 2010. https://doi.org/10.1017/CBO9780511750496.

Mrazek MF. Comparative Approaches to Pharmaceutical Price Regulation in the European Union. Croat Med J 2002;43:453–61.

Neumann PJ, Sc D, Cohen JT, Ph D. Measuring the Value of Prescription Drugs. Value-Based Cancer Care 2015;373:2595–7. https://doi.org/10.1056/NEJMp1508387.

Official Journal of the European Communities. The Charter of Fundamental Rights of the European Union. vol. 364. 2000. https://doi.org/10.1515/9783110971965.518.

Olry de Labry-Lima A, Ponce-Polo A, García-Mochón L, Ortega-Ortega M, Pérez-Troncoso D, Epstein D. Challenges for Economic Evaluations of Advanced Therapy Medicinal Products: A Systematic Review. Value Heal 2023;26:138–50. https://doi.org/10.1016/j.jval.2022.07.004.

Olsen JP. The many faces of Europeanizaton. J Common Mark, 2002;40(5):921-952.

Organisation WH. How to develop and implement a national drug policy. WHO Policy Perspect Med 2003;6:1–6.

Orsini LS, Monz B, Mullins CD, Brunt D Van, Daniel G, Jennifer HE, et al. Improving transparency to build trust in real-world secondary data studies for hypothesis testing — Why , what , and how : recommendations and a road map from the real-world evidence transparency initiative. Value Heal 2020;23:1128–36. https://doi.org/10.1002/pds.5079.

Pace A, Azzopardi LM, Serracino-Inglott A, Wismayer L, Adami MZ. DEVELOPMENT IN THE EUROPEAN UNION AND ACCESS TO MEDICINES. Pharm Glob Int J Compr Pharm 2013.

Pani L, Montilla S, Németh G, Russo P, Viceconte G, Vogler S. Balancing access to medicines and sustainability in Europe: An analysis from the network of competent

authorities on pricing and reimbursement (CAPR). Pharmacol Res 2016;111:247–50. https://doi.org/10.1016/j.phrs.2016.05.022.

Panteli D, Arickx F, Cleemput I, Dedet G, Eckhardt H, Fogarty E, et al. Pharmaceutical regulation in 15 European countries review. Health Syst Transit 2016;18:1–122.

Panteli D, Eckhardt H, Nolting A, Busse R, Kulig M. From market access to patient access: Overview of evidence-based approaches for the reimbursement and pricing of pharmaceuticals in 36 European countries. Heal Res Policy Syst 2015;13:1–9. https://doi.org/10.1186/s12961-015-0028-5.

Pearson SD, Ollendorf DA, Chapman RH. New Cost-Effectiveness Methods to Determine Value-Based Prices for Potential Cures: What Are the Options? Value Heal 2019;22:656–60. https://doi.org/10.1016/j.jval.2019.01.012.

Perehudoff K. Universal access to essential medicines as part of the right to health: a cross-national comparison of national laws, medicines policies, and health system indicators. Glob Health Action 2020;13. https://doi.org/10.1080/16549716.2019.1699342.

Perehudoff K, Durán C, Demchenko I, Mazzanti V, Parwani P, Suleman F, et al. Impact of the European Union on access to medicines in low- and middle-income countries: A scoping review. Lancet Reg Heal - Eur 2021;9. https://doi.org/10.1016/j.lanepe.2021.100219.

Perehudoff K, Forman L. What Constitutes “Reasonable” State Action on Core Obligations? Considering a Right to Health Framework to Provide Essential Medicines. J Hum Rights Pract 2019;11:1–21. https://doi.org/10.1093/jhuman/huz013.

Perehudoff S, Laing R, Hogerzeil H. Access to essential medicines in national constitutions. Bull World Health Organ 2006;84:371–5. https://doi.org/10.2471/BLT.06.031153.

Permanand G, Mossialos E, McKee M. Regulating medicines in Europe: The European Medicines Agency, marketing authorisation, transparency and pharmacovigilance. Clin Med J R Coll Physicians London 2006;6:87–90. https://doi.org/10.7861/clinmedicine.6-1- 87.

Persaud N, Jiang M, Shaikh R, Bali A, Oronsaye E, Woods H, et al. Comparison of essential medicines lists in 137 countries. Bull World Health Organ 2019;97:394-404C. https://doi.org/10.2471/BLT.18.222448.

Petry K, Maes B, Vlaskamp C. Operationalizing quality of life for people with profound multiple disabilities: a Delphi study. J Intellect Disabil Res 2007;51:334–49. https://doi.org/10.1111/j.1365-2788.2006.00882.x.

Piggott T, Nowak A, Brignardello-Petersen R, Cooke GS, Huttner B, Schünemann HJ, et al. Global status of essential medicine selection: A systematic comparison of national essential medicine lists with recommendations by WHO. BMJ Open 2022;12. https://doi.org/10.1136/bmjopen-2021-053349.

Pignatti F, Boone H, Moulon I. Overview of the European Regulatory Approval System. J Ambul Care Manag 2004;27:89–97.

Post C, Van Laarhoven HWM, Hollak C. Time to access to novel anticancer drugs in Europe , a case study in seven European countries . Jorunal Clin Oncol 2002;40:1586–7. https://doi.org/10.1200/JCO.2022.40.16.

Prescrire R. 2006 TRENDS A look back at pharmaceuticals in 2006 : 2007;27.

Quick JD, Hogerzeil H V., Velásquez G, Rägo L. Twenty-five years of essential medicines. Bull World Health Organ 2002;80:913–4.

Radaelli CM. Europeanization: Solution or Problem? Palgrave Adv Eur Union Stud 2006:56–76. https://doi.org/10.1057/9780230522671_4.

Reeves A, McKee M, Stuckler D. The attack on universal health coverage in Europe: Recession, austerity and unmet needs. Eur J Public Health 2015;25:364–5. https://doi.org/10.1093/eurpub/ckv040.

Roughead EE, Lopert R, Sansom LN. Prices for innovative pharmaceutical products that provide health gain: A comparison between Australia and the United States. Value Heal 2007;10:514–20. https://doi.org/10.1111/j.1524-4733.2007.00206.x.

Ruether A, Imaz-Iglesia I, Belorgey C, Lo Scalzo A, Garrett Z, Guardian M. European collaboration on health technology assessment : looking backward and forward. Int J Technol Assess Heal 2022;38:1–4.

Salisbury H. Helen Salisbury: Who let the drug companies in? BMJ 2019;365:2019. https://doi.org/10.1136/bmj.l1581.

Salmikangas P, Schuessler-Lenz M, Ruiz S, Celis P, Reischl I, Menezes-Ferreira M, et al. Marketing regulatory oversight of advanced therapy medicinal products (ATMPs) in europe: The EMA/CAT perspective. Adv Exp Med Biol 2015;871:103–30. https://doi.org/10.1007/978-3-319-18618-4_6.

Sarkis M, Bernardi A, Shah N, Papathanasiou MM. Emerging challenges and opportunities in pharmaceutical manufacturing and distribution. Processes 2021;9:1–16. https://doi.org/10.3390/pr9030457.

Schuster SJ, Tam CS, Borchmann P, Worel N, Mcguirk JP, Holte H, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas ( JULIET ): a multicentre , open-label , single-arm , phase 2 study. Lancet Oncol 2021;22:1403–16. https://doi.org/10.1016/S1470-2045(21)00375-2.

Scott J. A Matter of Record, Documentary Sources in Social Research. Cambridge Polity Press 1990.

Sermeus W, Gillet P, Gillain D, Grietens J, Laport N, Michiels D, et al. Development and validation of nursing resource weights for the Belgian Nursing Minimum Dataset in general hospitals: a Delphi questionnaire survey approach. Int J Nurs Stud 2009;46:256–67. https://doi.org/10.1016/j.ijnurstu.2008.09.007.

Sieveking K. ECJ rulings on health care services and their effects on the freedom of cross-border patient mobility in the EU. Eur J Migr Law 2007;9:25–51.

Simoens S, Abdallah K, Barbier L, Lacosta TB, Blonda A, Car E, et al. How to balance valuable innovation with affordable access to medicines in Belgium? Front Pharmacol 2022:1–17. https://doi.org/10.3389/fphar.2022.960701.

Smith S, Connolly S. Re-thinking unmet need for health care: Introducing a dynamic perspective. Heal Econ Policy Law 2020;15:440–57. https://doi.org/10.1017/S1744133119000161.

Soon JM, Davies WP, Chadd SA, Baines RN. A Delphi-based approach to developing and validating a farm food safety risk assessment tool by experts. Expert Syst Appl 2012;39:8325–36. https://doi.org/10.1016/j.eswa.2012.01.189.

Stadhouders N, Koolman X, Tanke M, Maarse H, Jeurissen P. Policy options to contain healthcare costs: A review and classification. Health Policy (New York) 2016;120:486–94. https://doi.org/10.1016/j.healthpol.2016.03.007.

Stephens J, Hanke, Doshi J. International survey of methods used in health technology assessment (HTA): does practice meet the principles proposed for good research? Comp Eff Res 2012;2:29–44. https://doi.org/10.2147/cer.s22984.

Steurer J. The Delphi method: an efficient procedure to generate knowledge. Skeletal Radiol 2011;40:959–61. https://doi.org/10.1007/s00256-011-1145-z.

Syn NLX, Yong WP, Goh BC, Lee SC. Evolving landscape of tumor molecular profiling for personalized cancer therapy: a comprehensive review. Expert Opin Drug Metab Toxicol 2016;12:911–22. https://doi.org/10.1080/17425255.2016.1196187.

Taghreed A, De Savigny D. Systems Thinking for Health Systems Strengthening. Geneva: World Health Organization; 2010. https://doi.org/10.4037/CCN2022225.

Taglione MS, Persaud N. Assessing variation among the national essential medicines lists of 21 high-income countries: A cross-sectional study. BMJ Open 2021;11. https://doi.org/10.1136/bmjopen-2020-045262.

Țăran AM, Mustea L, Vătavu S, Lobonț OR, Luca MM. Challenges and Drawbacks of the EU Medical System Generated by the COVID-19 Pandemic in the Field of Health Systems' Digitalization. Int J Environ Res Public Health 2022;19. https://doi.org/10.3390/ijerph19094950.

Thomson S, Foubister T, Mossialos E. Financing health care in the European Union: Challenges & Policy Responses. Health Aff 2009;29:217.

Tobbell DA. "Who's winning the human race?" Cold war as pharmaceutical political strategy. J Hist Med Allied Sci 2009;64:429–73. https://doi.org/10.1093/jhmas/jrp012.

Towse A, Fenwick E. Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment? Value Heal 2019;22:677–83. https://doi.org/10.1016/j.jval.2019.03.013.

Trish G. Evidence debased medicine. BMJ 2010;341:787. https://doi.org/10.1136/bmj.c5641.

Turenne CP, Gautier L, Degroote S, Guillard E, Chabrol F, Ridde V. Conceptual analysis of health systems resilience: A scoping review. Soc Sci Med 2019;232:168–80. https://doi.org/10.1016/j.socscimed.2019.04.020.

United Nations Secretary Generals. Report of the United Nations Secretary - General's High-Level Panel on Access to Medicines. Promoting innovation and access to health technologies. High-Level Panel Access to Heal Technol 2016.

Uyl-De Groot CA, Heine R, Krol M, Verweij J. Unequal access to newly registered cancer drugs leads to potential loss of life-years in europe. Cancers (Basel) 2020;12:1–17. https://doi.org/10.3390/cancers12082313.

Uyl-de Groot CA, de Vries EGE, Verweij J, Sullivan R. Dispelling the myths around cancer care delivery: It's not all about costs. J Cancer Policy 2014;2:22–9. https://doi.org/10.1016/j.jcpo.2014.01.001.

Vargas-Peláez CM, Rover MRM, Leite SN, Rossi Buenaventura F, Farias MR. Right to health, essential medicines, and lawsuits for access to medicines - A scoping study. Soc Sci Med 2014;121:48–55. https://doi.org/10.1016/j.socscimed.2014.08.042.

Viergever RF. The mismatch between the health research and development (R&D) that is needed and the R&D that is undertaken: an overview of the problem, the causes, and solutions. Glob Health Action 2013;6:22450. https://doi.org/10.3402/gha.v6i0.22450.

Vogler S, Habl C, Bogut M, Vončina L. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. Croat Med J 2011;52:183–97. https://doi.org/10.3325/cmj.2011.52.183.

Vogler S, Österle A, Mayer S. Inequalities in medicine use in Central Eastern Europe: An empirical investigation of socioeconomic determinants in eight countries. Int J Equity Health 2015;14. https://doi.org/10.1186/s12939-015-0261-0.

Vogler S, Paris V, Ferrario A, Wirtz VJ, de Joncheere K, Schneider P, et al. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. Appl Health Econ Health Policy 2017;15:307– https://doi.org/10.1007/s40258-016-0300-z.

Vokinger KN, Hwang TJ, Glaus CEG, Kesselheim AS. Therapeutic Value Assessments of Novel Medicines in the US and Europe, 2018-2019. JAMA Netw Open 2022;5:E226479. https://doi.org/10.1001/jamanetworkopen.2022.6479.

Vreman RA, Mantel-Teeuwisse AK, Hovels AM, Leufkens HGM, Goettsch WG. Differences in Health Technology Assessment Recommendations Among European Jurisdictions: The Role of Practice Variations. Value Heal 2020;23:10–6. https://doi.org/10.1016/j.jval.2019.07.017.

Wach K. Europeanisation: Its Definition, Research Approaches and Dimensions. In: Stanek P, Wok K, editors. Macro-, Meso-, and Microeconomic Dimensions of Europeanisation. 1st ed. Warsaw: Wydawnictwo Naukowe PWN SA; 2016. p 15-32

Waddington PAJ, Bull R. Cognitive Interviewing as a Research Technique. Soc Res Updat, 2007;50(1):4.

Wahlster P, Scahill S, Lu CY, Babar ZUD. Barriers to access and use of high cost medicines: A review. Heal Policy Technol 2015;4:191–214. https://doi.org/10.1016/j.hlpt.2015.04.009.

Walliman N. Research Methods: The Basics. 2nd ed. London: Routledge; 2017. Warren-jones A. Health care and health innovation in Europe : regulating for public benefit or for commercial profit ? Heal Econ Policy Law 2017;12:403–9. https://doi.org/10.1017/S1744133117000081.

WHO. Global strategy and plan of action on public health, innovation and intellectual property. Sixty-first World Health Assembly, 19–24 May 2008, Resolution WHA61.21. World Heal Organ 2008.

WHO. Equitable access to essential medicines: a framework for collective action. WHO Policy Perspect Med 2004;March:1–6.

Wieseler B, McGauran N, Kaiser T. New drugs: Where did we go wrong and what can we do better? BMJ 2019;366:1–8. https://doi.org/10.1136/bmj.l4340.

Wilking N, Bucsics A, Kandolf Sekulovic L, Kobelt G, Laslop A, Makaroff L, et al. Achieving equal and timely access to innovative anticancer drugs in the European Union (EU): Summary of a multidisciplinary CECOG-driven roundtable discussion with a focus on Eastern and South-Eastern EU countries. ESMO Open 2019;4:1–10. https://doi.org/10.1136/esmoopen-2019-000550.

Wilking N, Jönsson B. A pan-European comparison regarding patient access to cancer drugs. Stockholm: 2005.

Wirtz VJ, Hogerzeil H V., Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, et al. Essential medicines for universal health coverage. Lancet 2017;389:403–76. https://doi.org/10.1016/S0140-6736(16)31599-9.

World Health Organisation. European Region. Final Report of the Oslo Medicines Initiative. Improving access to novel , high-priced medicines in the WHO European Region. 2022.

World Health Organization. WORLD HEALTH STATISTICS - MONITORING HEALTH FOR THE SDGs. World Heal Organ 2016:1.121.

Wouters OJ, Berenbrok LA, He M, Li Y, Hernandez I. Association of Research and Development Investments With Treatment Costs for New Drugs Approved From 2009 to 2018. JAMA Netw Open 2022;5:E2218623. https://doi.org/10.1001/jamanetworkopen.2022.18623.

Yeung K, Suh K, Garrison LP, Carlson JJ. Defining and Managing High-Priced Cures: Healthcare Payers' Opinions. Value Heal 2019;22:648–55. https://doi.org/10.1016/j.jval.2018.11.012.

Zamora B, Maignen F, O'Neill P, Mestre-Ferrandiz J, Garau M. Comparing access to orphan medicinal products in Europe. Orphanet J Rare Dis 2019;14:1–13. https://doi.org/10.1186/s13023-019-1078-5.

# Appendix 1: Invitation Letter for Participants & Ethics Approval

## Appendix 1A: Ethics Approval

### FREC MDS_1920_194 - UNIQUE FORM ID: 5783_20062020_Lilian Wismayer

Dear Ms Wismayer,

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

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

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

These documents are also requested for audit purposes.

Regards,

L-Università ta' Malta

**Ruth Stivala** | Secretary
B.A.(Hons)(Melit.),M.A.(Melit.)

**Faculty Research Ethics Committee**
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1214

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

**Appendix 1B: Invitation Letter for Participants**


DATE

Dear _____

I am currently reading for a degree in Doctor of Philosophy (PhD) with the Department of Pharmacy, University of Malta, under the supervision of Prof. L. M. Azzopardi (lilian.m.azzopardi@um.edu.mt). This study, entitled *Pharmaceutical Regulation, Policy and Access to Medicines*, has the aim of identifying and evaluating issues related to Access to Medicines (ATM), and proposing a framework which may be used to improve ATM to patients.

Access has been defined as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk of the population" (United Nations Development Group. Indications for monitoring the Millennium Development Goals. New York; United Nations; 2009). ATM indicators include:

- Physical access to medicines and "essential drugs";
- Financial access reflecting cost and affordability;
- Rational prescribing and use;
- Access to information on medicinal products and treatment options.

I would like to invite you to participate in this research. Your input would be of great value in view of your expertise and experience. Your participation is entirely voluntary. Should you wish to withdraw at any time, date gathered from you would be deleted.

All data collected will be used solely for the purpose of this study, will be treated with confidentiality and will be anonymous. It will be categorised according to the field of expertise of the participant and stored in accordance with General Data Protection Regulation (GDPR). All data will be deleted within five years. The results of the research may be published scientifically.

Under GDPR, you have the right to access, rectify and request the deletion of the data concerning you. Your participation does not entail any known or anticipated risks, neither are there any direct benefits to you.

_____

Lilian Wismayer

# Appendix 2: Questionnaire to Pharmacists

# Questionnaire to Pharmacists

SECTION A

1) Are you?

- Female
- Male
- Other
- Prefer not to say

2) How old are you?

- <45
- 45 plus

3) How many years of working experience have you had?

4) Which of the following areas have you worked in?

- Community pharmacy
- Hospital pharmacy
- Regulation
- Other

SECTION B

5) What do you understand by Access to Medicines?

*After the respondent answered Question 1, the researcher read out the definition of Access to Medicines, as defined in Appendix 1B, and provided a hardcopy for reference.*

6) Does the reimbursement system for medicines on the NHS work effectively in ensuring access?

   Yes No

7) Does the range of medicines available on the NHS fulfil the criterion of appropriate access to medicinal products?

   Yes No

8) What barriers to Access to Medicines have you experienced in your practice?

9) In relation to medicines' use, are there therapeutic guidelines, protocols, pharmaceutical policy and/or a mechanism through which problems regarding Access may be raised and addressed?

10)

a. Do you experience problems with dispensing prescriptions to EU nationals from other Member States?

Yes No

b. If yes, is there a methodology or procedure that you follow when faced with such problems?

11) Do you have any other comments that you wish to make?

# Appendix 3: Unstructured Interview with Doctors & Nurses

**Access to Medicines: The Perspective of Doctors and Nurses in Health Care Provision**

**Unstructured Interview**

Opening Statement for Interview:

Timely Access to Medicines is seen, today, as an important parameter in effective health care provision. Based on your professional experience in the field, what are the issues that you encounter in this regard?

DISCUSS

# Appendix 4: Questionnaire to Prescribers

## Access to Medicines: Questionnaire to Prescribers

Rational prescribing incorporates the selection of the most appropriate therapy (achieving maximal clinical effectiveness and minimal harm) whilst avoiding resource wastage.

Two outcomes should, therefore, result from rational prescribing:

i. evidence-based optimal patient care
ii. at the lowest possible cost.

It is considered an important component of cost-effectiveness, managing paramount use of financial resources, and may be regarded as a major indicator of economic accessibility.

1) On average, how often have you received information and/or educational material regarding the rational prescribing of medicines over the last twelve months?

Never ___

1 – 4 times ___

More than 4 times ___

2) How many training sessions which included medicines' use were available to you over the last twelve months?

None ___

1 – 4 sessions ___

More than 4 sessions ___

3) Is advice on national Standardised Therapy Guidelines / Protocols readily available to you?

Yes ____ No ____

4) Are you aware of any Drug Utilisation Evaluations carried out within the National Health Service?

Yes ____ No ____

5) Do you receive feedback on the utilisation of medicinal products within the National Health System?

Yes ____ No ____

6a) Have you experienced any initiatives targeting the modification of prescribing behaviour?

Yes ____ No ____

6b) If yes, do you feel that these were successful in the long term?

Yes ____ No ____

7) Does the National Health System allow prescribers to be actively involved in the choice of medication available on the formulary?

Yes ____ No ____

8a) Are you aware of the procedures / decision-making process used for new medicinal products to be included in the formulary?

Yes ____ No ____

8b) If yes, do you feel that this process:

- is effective? Yes ____ No ____
- provides feedback? Yes ____ No ____

9) By what means do you become aware of changes to the formulary?

- I am personally notified Yes ____ No ____ Comment _____
- Word of mouth Yes ____ No ____ Comment _____
- Official email/letter Yes ____ No ____ Comment _____
- Other (please specify) _____

10) What are your sources of information regarding medicinal products? Tick as necessary.

- Medical representatives _____
- Summary of product characteristics _____
- Drugs and Therapeutics Committee _____
- Other (please specify) _____

11) Do you have any comments?

_____

# Appendix 5: Semi-Structured Interview - Health Care Provision

## Access to Medicines: The Health Care Provision Perspective

## Semi-Structured Interview

1) What, in your experience, are the main barriers to Access to Medicines?

2) What, in your experience, are the main barriers to their rational and effective use?

3) Does existing policy (national and EU) cater to overcoming these barriers?

4) Does the existing policy / regulatory infrastructure cater for cross-border access?

5) What are the existing obstacles that you face and how can the system be improved?

6) Can you describe the pricing review process? (obstacles/improvements)

7) Can you describe the current/planned systems addressing health technology assessment? (obstacles/improvements)

8)
    a. What kind of problems are encountered when there is a lack of availability?
    b. Can you highlight areas of improvement?
    c. Are the causes (shortages) reviewed / analysed?

9)
    a. Are you aware of any problems that patients can encounter as a result of a lack of good practice and excessive bureaucracy?
    b. Do you have any recommendations for improvement?

10) When making choices regarding medicinal products and access to them, is there any correlation with:
    a. Disease incidence?
    b. Prevalence within HTA?
    c. Burden?

11) Does the system allow for rapid identification of public health / unmet needs?

12) Do you have any other comments you wish to make?

# Appendix 6: Semi-Structured Interview - Payer Advocacy

## Access to Medicines: The Payer Advocacy Perspective

## Semi-Structured Interview

1) Are Health Technology Assessments (HTAs) an ideal tool to assess clinical value?
2) Can we increase the capacity for Quality measurement?
3) Do HTAs reflect the individual needs of patients who often respond differently to medicines (based on factors such as age, genetics, co-morbidities)?
4) Can we break up HTAs into a two-step process: one that incorporates common parameters across all Member States, and another that adapts the final assessment to individual Member States requirements?
5) Our health care systems are becoming increasingly value-driven. Do current pharmaceutical policy models support any of the following?
    a. Equitable and timely patient access to medicinal products immediately upon the grant of a marketing authorisation;
    b. Rational use of a medicinal product upon the grant of a marketing authorisation;
    c. Evaluation of evidence supporting the medicine's clinical value upon use (close audit loop). Can this be linked to reimbursement / reward to the industry?
    d. Controlling costs.
6) Do European Competent Authorities share information reflecting the medicine's clinical value with payers / insurers / health care providers effectively?
7) Should regulatory assessment by Competent Authorities in the EU include expected outcomes on the patient population?
   *(e.g.: results of pharmacoeconomic studies, reduced hospital admissions, reduced surgical interventions, reduced monitoring)*
8) Do any rebound effects occur when medicines are placed / not placed / delayed being placed on the positive list?
9) A number of Member States (including Malta) fail to achieve the 180-day limit imposed by the Transparency Directive.
    a. What are the consequences to this in real terms to patients, and with regards to market access rules?
    b. Is there a rebound effect on the private sector?
10) What other models of operation may exist in the national pharmaceutical sector?
    *(e.g. recent proposal to remove copaid medicines from the Community Chest Fund financing)*

11) What pharmaceutical policy determinants do you identify and what would be the related expected outcome?

    *(This question should be taken from its wider perspective and also in terms of the expected responsibilities implied in EU legislation / norms.)*

12) How would you define payer advocacy parameters in the context of the previous question?
13)
    a. There are current proposals to:
        i. Further modify time limits set in the Transparency Directive;
        ii. Alter pathways related to market access.
    b. What expected impact is there from the payer advocacy perspective?
14) Do you feel that medicinal product status (OTC / POM) should be altered to improve patient access?
15)
    a. Budgetary limitations remain a very real constraint in this scenario, and a number of countries are searching for innovative solutions in this regard.
    b. Can you comment keeping in mind the newer therapeutic technologies?
16) Pricing is inevitably linked to costs. There is also an inversely proportionate relationship between costs and access. Can you comment?
17) Do you have any other comments you wish to make?

# Appendix 7: Semi-Structured Interview - Health Economics

## Access to Medicines: The Health Economics & Financial Perspective

## Semi-Structured Interview

1) Do you feel that current systems and policies ensure best practice economic evaluation of medicinal products in the natural health system?
2) Do pricing mechanisms result in fair, cost-effective results and outcomes?
3) Do policy decisions regarding the reimbursement of medicinal products support timely access to appropriate therapeutic options?
4)
    a. How are budgetary allocation decisions taken?
    b. Is there feedback on results and outcomes?
    c. What problems are experienced in this regard?
5) Do you feel that co-financing mechanisms produce more positive cost-effectiveness?
6) Can policies regarding the pharmaceutical models of care adopted impact market size and marketing interest in the smaller Member States?
7) Which methodologies would you propose to improve:
    a. Optimal decision-making;
    b. Optimal use of resources?
8)
    a. Are there effective communication lines between payers and policy-makers?
    b. Are these based on a fundamental understanding of each other's roles and responsibilities?
9) Do you feel that payers' (on budgetary allocations) expectations such as those listed below should be and are being addressed?
    - rational use of financial resources
    - predictability and forward planning
    - regular plans and reports (including statistical)
    - cost-effectiveness and efficiency (wastage, shortages)
    - other.

10) Do you feel that health-care providers / policy-makers should have expectations such as those listed below from payers' (on budgetary allocations):
    - clear rules and objectives
    - financial provision "rewards"
    - policy and long-term strategy
    - other
11) Do you feel that medicines' shortages in the National Health System are due to:
    - poor planning
    - global issues
    - logistical problems (access to precise information, limited sources, market size, etc)
    - other
12) Do you have any other comments you wish to make?

# Appendix 8: Semi-Structured Interview - Policy and Regulation

## Access to Medicines: The Policy and Regulatory Perspective

## Semi-Structured Interview

1)

a) Has Malta drafted, adopted or implemented a National Drug Policy (NDP)?

*(The scope of a NDP is to provide an overall guide for the formulation of strategies and action in this field)*

b) If not do you see advantages in establishing an NDP?

*...Which problems may it mitigate?*

*...Should it be transposed into law? (The Medicines Act).*

2) What should be the objective of an NDP?

*....To ensure the AVAILABILITY of safe and effective medicines of good quality to the population,*

*...based on the real health needs (do we know these?)*

*...and taking into consideration the prevailing disease pattern (do we know this?)*

*...and based on health development programmes in Malta (do we know which these are, if any)*

3) Are you aware of any initiatives or tools currently being used (by the Health Department, Drugs and Therapeutics Committee, the Competent Authority...) to:

- ensure rational prescribing
- monitor rational prescribing
- promote rational prescribing

4) Are all medicinal products purchased for the National Health System (NHS) registered? (have a marketing authorisation)

5)

a) Does the system for the selection of medicines for inclusion into the positive list (formulary) successfully address:

- the prioritisation of real health care needs
- equitability
- sustainability
- the needs of the most vulnerable
- cost effectiveness
- other

b) What problems are encountered?

c) How can the system/process be improved?

6)

a) Are medicines on the NHS used

- efficiently (e.g.: hoarding)
- rationally

b) What improvements do you suggest?

7)

a) Is there a Drug Information System?

b) Does it take effective and/or pro-active measures to

- inform
- educate
- communicate

with health care professionals_____ with the public_____

8)

a) In your opinion, is the use of ESSENTIAL drugs is promoted/encouraged in the

- private health sector?
- public health sector?

b) Should this be done? Why? How?

9)

a) In your opinion, do the pharmaceutical services, at a national level, ensure consumer protection in all areas/activities regarding medicines?
*(in-patient care, point-of-care, counselling, community/ primary care)*

b) How can this be improved?

10) Is the potential of the pharmaceutical sector, at a national level,

- explored
- encouraged

*E.g.: in Manufacturing, clinical pharmacy*

11) Are Standard Treatment Guidelines

- adopted (by whom?)
- made available (to whom?)
- readily accessible (to whom?)

...in the public health sector _____ private health sector _____

12)

a) Is the process for the inclusion of medicines into the formulary/positive list
   - well documented
   - transparent
   - efficient
   - pro-active or reactive
   - feedback is given (by/ to whom?)
   - differentiates between primary and secondary care
   - post-approval audits are carried out

b) What are the problems?

c) How can it be improved?

13)

a) In your opinion, is the availability of essential medicines is effectively ensured in the
   - private sector
   - public sector

b) What are the problems?

c) How can this be improved?

14) Is there any particular consideration being given to new, innovative, high-cost medication expected to come onto European markets in the future?

15) Is effective generic substitution achieved in the private sector?

16) Does incoming EU legislation act as a trigger to review medicines on the positive list?
*(e.g. Trade policies, cross-border health care)*

17)

a) Are there circumstances when EU pharmaceutical legislation unintentionally results in creating obstacles to, or in effectively reducing, Access to Medicines?
   (Falsified Medicines Directive, in terms of cost, in terms of reducing parallel trade, Orphan medicinal products)

b) How can this be overcome?

c) Is there enough consideration given to the smaller states?

d) Are there initiatives in this regard?

18) Can EU legislation be modified to improve Access to Medicines, particularly in the less attractive markets? *(Sundowning clause in centralised procedure)*

19) Are EU initiatives regarding Access to Medicines giving tangibly positive results?

20) Can the health care system be re-engineered such that Access to Medicines is improved?

# Appendix 9: The Focus Group

## Appendix 9A: Information Sheet and Consent Form


**Information Sheet**

for prospective participants in the research titled

"**Pharmaceutical Regulation, Policy and Access to Medicines**"

Investigator: Lilian Wismayer
Institution: University of Malta
Project: PhD by research
Title: **Pharmaceutical Regulation, Policy and Access to Medicines**
Methodology: Focus Group
Supervisors: Prof Lilian Azzopardi and Dr Maurice Zarb Adami

I am currently reading for a degree in Doctor of Philosophy (PhD) with the Department of Pharmacy, University of Malta, under the supervision of Prof. L. M. Azzopardi (lilian.m.azzopardi@um.edu.mt). This study, entitled *Pharmaceutical Regulation, Policy and Access to Medicines*, has the aim of identifying and evaluating issues related to Access to Medicines (ATM), and proposing a framework which may be used to improve ATM to patients.

Access has been defined as "having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk of the population" (United Nations Development Group. Indications for monitoring the Millennium Development Goals. New York; United Nations; 2009).

ATM indicators include:

- Physical access to medicines and “essential drugs”;
- Financial access reflecting cost and affordability;
- Rational prescribing and use;
- Access to information on medicinal products and treatment options.

I invite you to participate in this research. Your input would be of great value in view of your expertise and experience. Your participation is entirely voluntary. Should you wish to withdraw at any time, date gathered from you would be deleted.

All data collected will be used solely for the purpose of this study, will be treated with confidentiality and will be anonymous. It will be categorised according to the field of expertise of the participant and stored in accordance with General Data Protection Regulation (GDPR). All data will be deleted within five years. The results of the research may be published scientifically.

Under GDPR, you have the right to access, rectify and request the deletion of the data concerning you. Your participation does not entail any known or anticipated risks, neither are there any direct benefits to you.

Lilian Wismayer

**Certificate of Consent**

for prospective participants in the research titled

"**Pharmaceutical Regulation, Policy and Access to Medicines**"

Investigator: Lilian Wismayer
Institution: University of Malta
Project: PhD by research
Title: **Pharmaceutical Regulation, Policy and Access to Medicines**
Methodology: Focus Group
Supervisors: Prof Lilian Azzopardi and Dr Maurice Zarb Adami

I hereby consent to participate in a Focus Group related to my expertise and experience in pharmaceutical regulation and/or policy, and/or the pharmaceutical industry.

I have read the Information Sheet attached. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.

I consent voluntarily to be included as participant in this study.

Name _____

Signature _____

Date _____

## Appendix 9B: Background Document

L-Università ta' Malta

**Background to the Focus Group**

for participants in the research titled

"**Pharmaceutical Regulation, Policy and Access to Medicines**"

Investigator: Lilian Wismayer

Institution: University of Malta

Project: PhD by research

Title: **Pharmaceutical Regulation, Policy and Access to Medicines**

Methodology: Focus Group

Supervisors: Prof Lilian Azzopardi and Dr Maurice Zarb Adami

Figure A illustrates how a European Access Framework may support the entry and rational use of medicinal products into the national health system. Member State adaptation of the Access Framework should be delineated by the National Medicines Policy.

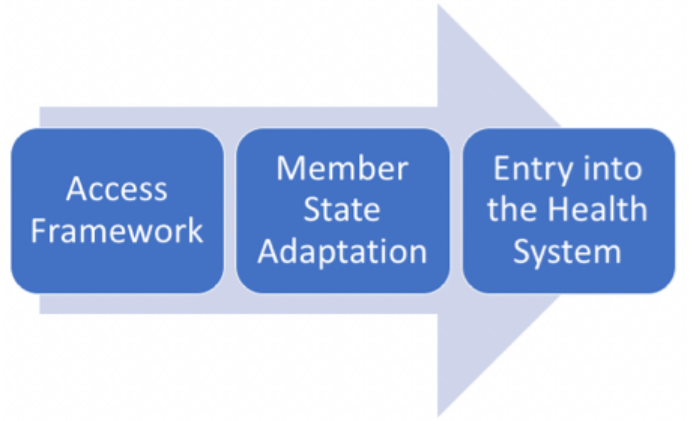


*Figure A: The Access Framework within a European Model*

The findings of this research highlight that the Access Framework should not only target entry but should also include monitoring and audit of the actual outcomes, as indicated in Figure B.

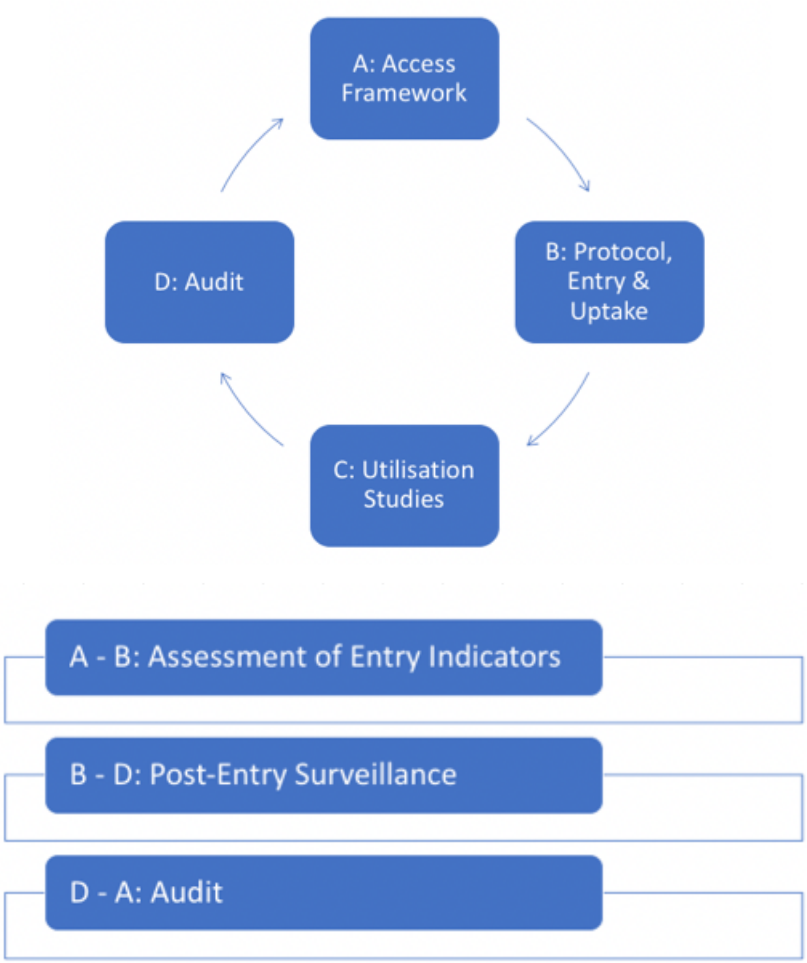


*Figure B: Utilisation of the Access Framework*

The process delineating the Access Framework is shown in Figure B. It demonstrates how the Framework may be utilised to support the rational use of medicines and effective outcome measurement.

Through this study, Access To Medicines indicators were identified and categorised into four distinct dimensions or domains, as presented in Table A. This provides the basis for an Access Framework.

| Access Framework | |
|---|---|
| Dimension | Indicators |
| Uptake | • Pricing / Reimbursement<br>• Forecasted cost-effectiveness / Therapeutic value<br>• Prospective public health gains (health strategy, data regarding prevalence)<br>• Projected budgetary impact<br>• Affordability / Sustainability |
| Utilisation | • Availability / Shortages<br>• Rational use: protocols / national treatment guidelines<br>• Rational prescribing<br>• Dispensing / counselling<br>• Public Campaigns (educational material)<br>• Feedback from health care professionals and patients |
| Audit | • Prescribing or dispensing database incl. patient numbers<br>• Actual reimbursement and expenditure data<br>• Utilisation studies targeting evidence-based treatment outcomes |
| Re-Evaluation | • Audit results: do these correspond to the expected cost-effectiveness and public health gains?<br>• Does the medicinal product satisfy the Access Framework indicators?<br>• Should treatment guidelines and protocols be re-appraised? |

*Table A: An Approach to the Entry and Utilisation of Medicinal Products in a National Health System*

Each dimension denotes a type of activity which collectively, if staged and linked chronologically, enable a continuous evaluation and re-evaluation of the medicinal product.

Aims of the Focus Group:

- Comment on the application and the practical implications of the proposed Framework
- Identify issues such as weaknesses and limitations of the Framework
- Provide feedback on the study findings

## Appendix 9C: Discussion Guide


**Pharmaceutical Regulation, Policy and Access to Medicines**

**Focus Group Discussion Guide**

The Access Framework has been designed with the intention of being flexibly applied by the individual member states whilst being coordinated and supported by the European Commission, with the intention of achieving an increasingly harmonised approach to Access to Medicines.

1. List 3 points regarding the application and practical implications of this proposal to be collectively discussed by the group.
2. During the ensuing discussion by the group, consider which indicators should be supported/co-ordinated by the European Commission.
3. List at least 1 strength, 1 weakness, 1 opportunity and 1 threat related to the proposed Access Framework.
4. Suggest examples or test cases for the Access Framework considering case studies of medicinal products you have experience of.
5. Any other general feedback you may have regarding the study findings would be appreciated.

Thank you.

# Appendix 10: Publications

**Conference Proceedings:**

- Wismayer, L., Zarb Adami, M., Azzopardi, L.M. 'Pharmaceutical Regulation, Policy and Access to Medicines in the European Union', 80th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences. 2022 September 18-22. Seville, Spain.

Citation:

FIP Seville conference abstracts 2022 Regulatory Sciences and Quality Pharmacy Education 23(3)308-317

https://doi.org/10.46542/pe.2023.233.308317

specific quality procedures for each equipment and the activities carried out.

**Results**: The general quality procedure describes the acquisition, reception and dispensing of medicines and medical devices. They are made through a computer programme and in paper format with official requests. For the dispensing of specially controlled medications (psychotropic and narcotic) we have internal dispensing orders.

Among the specific procedures for the formulation laboratory, the workflow that must be carried out to ensure the correct storage of any test items. Entry and exit registers, temperature control and locked storage. The order specific procedures focus on the usefulness and handling of the specific equipment.

**Conclusions**: The importance of quality management and the need to have standard procedures for the different talks carried out, help to protocolize and improve the operation of the pharmacy services and its involvement in different research projects.

## Good laboratory practice in a research clinical analysis laboratory

Beatriz Moreno Lobato[1*], Natalia Picado Román[2], Jorge Bote Chacón[3], Francisco Miguel Sánchez Margallo[3]

[1]*Animal Model Service, Spain*

[2]*Pharmacy Service, Spain*

[3]*Scientific Director, Spain*

** bmorenolobato@ccmijesususon.com*

**Background:** Good Laboratory Practices (GLP) is a quality system that involves the organisation of a research laboratory. In order to control the entire clinical analysis process, it is essential that the laboratory is equipped with, applies and maintains a quality system. Its compliance is a minimum requirement that clinical laboratories must meet to increase adherence to standardised practices and procedures and improve the delivery of reproducible and reliable results, while ensuring safety.

**Objectives:** In order to correctly use and interpret a laboratory analysis and the results obtained, it was necessary to validate the analytical techniques performed in our laboratory before using them routinely in order to guarantee the analytical results performed in preclinical research studies.

**Methods**: For the implementation of Good Laboratory Practices the validation of all analytical methods routinely used in the clinical analysis laboratory of the Jesús Usón Minimally Invasive Surgery Center (CCMIJU) was carried out. The validation parameters measured were the intermediate precision and repeatability of the method. The study was performed on each analytical parameter in the different species used in preclinical studies, including hematological and biochemical parameters.

**Results**: : With the results obtained from the analytical validation, the statistical study was carried out and a verification report was written. The results obtained show that the degree of dispersion and the degree of concordance of the results obtained between a series of measurements obtained from multiple sampling of a homogeneous sample of each species studied under the prescribed conditions are good and reproducible.

**Conclusions**: The analytical method used to determine the blood parameters of the different species studied and analysed in the Clinical Analysis Laboratory of the CCMIJU is repetitive and reliable, considering that the preclinical studies carried out are safe, verifying the quality of the results obtained in our laboratory under GLP regulations.

## Pharmaceutical regulation, policy and access to medicines in the European Union

Lilian Wismayer*, Maurice Zarb Adami, Lilian Azzopardi

[1]*University of Malta, Malta*

** lilian.wismayer@um.edu.mt*

**Background:** European health systems have traditionally aimed at the provision of high-quality care and equity of access. This has become increasingly challenging over the past decades, with unabated pressure to deliver more and better services with insufficient resources. More specifically, in the pharmaceutical arena, there is growing concern and interest in the area of access to medicines in the European Union. Whilst member states are bound by a legislative infrastructure which addresses the quality, safety and efficacy of medicinal products on the market, patients in these territories experience disparate levels of access to these therapies. Paradigms for improvements in this field most often focus on the individual barrier and do not relate to the wider perspective.

**Objectives:** To investigate stakeholders' perceptions of barriers to medicines' access and to examine the influence of pharmaceutical policy and regulation in this area.

**Methods**: A systematic mixed-method approach was adopted, primarily comprising qualitative techniques. The study incorporated unstructured interviews with doctors and nurses, questionnaires to pharmacists and to prescribers and semi-structured interviews with experts seeking their perspectives on health care provision, payer advocacy, health economics, pharmaceutical policy and pharmaceutical

regulation. A focus group was conducted with the aim of consolidating and validating the findings and proposals of the study. Directed content analysis was used to evaluate and interpret the results. The initial coding guide was developed through the literature review. As the analysis evolved the coding scheme was reviewed and modified to embrace the differentiated categories of data.

**Results**: Deterrents to medicines' access are entrenched, and sometimes replicated, at various strata of the health systems of the member states. The advantages that a documented national medicines policy may bring in this context are not fully understood or implemented. The multiplicity of factors impacting access are also over-arching at a pan-European level. It would be difficult for a pan-European policy targeting access to medicines to accommodate the wide spectrum of divergences between the member states. Additionally the consensus in the member states is that Europeanisation of the pharmaceutical arena should not be further developed at this time. However the European Union's potential for providing technical support, networking and co-operation, establishing scientific norms, capacity building and the co-ordination and dissemination of information, should be exploited. The current initiative by the European Union to revise the legislation should strategise access to medicines as a focal point.

**Conclusions**: Measures to mitigate the challenge of medicines' access are best taken conjointly at European Union level and in the member states. The latter should adopt a transparent, cohesive and documented national policy which explicitly upholds access to medicines, provides clear direction and serves as a platform towards fostering this goal. To be fit for purpose, such a policy must be participative and inclusive of all actors and must be developed in accordance to each country's needs and resources. The Commission has a role in supporting and complementing the member states by developing generic facilitating frameworks.

## Exploring Mongolian healthcare professionals' experience adverse drug reaction reporting: Part of a questionnaire survey

Munkhnasan Purevjav[1*], Zuzaan Zulzaga[2], Erdenetuya Myagmarsuren[3]

[1]Department of Clinical Pharmacy and Management, School of Pharmacy, MNUMS, Mongolia

[2]Association Of Mongolian Pharmacy Professionals, Mongolia

[3]Department of Pharmacy, Mongol-Japan Hospital, MNUMS, Mongolia

* munkhnasan.p@gmail.com

**Keywords:** Adverse drug reaction reporting

**Background:** Spontaneous reporting of adverse drug reactions (ADRs) is a main regulatory approach of monitoring the medicines safety in the market. Current regulation requires each suspected case of ADR should be reported by healthcare professionals to the Medicine, medical devices regulatory agency. This study has evaluated existing practices by various levels of healthcare professionals for their implementation of current regulation on medicines safety.

**Objectives:** Aim of this study is to evaluate existing practice being implement ADR reporting procedure by health professionals at different health organisations.

**Methods**: The study is a qualitative and questionnaire survey containing 56 questions to evaluate sociodemographic characteristics, knowledge, attitude, practice behaviours of health professionals for ADR reporting and information. A sampling attendee was collected among physicians, pharmacists and nurses working in state and private hospitals, clinics, and pharmaceutical companies. Due to pandemic, data was collected by both approach paper and online-based way from May to September 2021. To process data, Stata 13 and MS Excel programmes were used.

**Results**: Of the total 1450 questionnaires distributed in urban and rural health organisations, 1199 health care professionals responded to the questionnaire (82.62% response rate). Among all healthcare professionals, nurses (40.53%) had a better attitude to respond in questionnaires. Total of 79.15% of respondents assumed that ADR reporting is advantageous, and that's the most high-rated response out of the total questions. Total of 53.71% of respondents assumed that Reporting of ADRs is not encouraged by someone, and that's the second high-rated response out of the total questions.

**Conclusions**: As initial result of the study, although most of health care professionals tend to support ADR reporting due to understand the importance of the reporting, they need more motivation to effective implementation of the existing procedure.

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

# Pharmaceutical regulation, policy and access to medicines in the European Union

Lilian Wismayer, Maurice Zarb Adami, Lilian M. Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

E-mail: lilian.wismayer@um.edu.mt

## INTRODUCTION

European health systems have traditionally aimed at the provision of high-quality care and equity of access. This has become increasingly challenging over the past decades, with unabated pressure to deliver more and better services with insufficient resources[1].

In the pharmaceutical arena, there is growing concern and interest in the area of access to medicines in the European Union. Whilst member states are bound by a legislative infrastructure which addresses quality, safety and efficacy of medicinal products on the market, patients in these territories experience disparate levels of access to medicines[3].
Paradigms for improvements in this field most often focus on the individual barrier and do not relate to the wider perspective[2].

## AIMS

To investigate stakeholders' perceptions of barriers to medicines' access and to examine the influence of pharmaceutical policy and regulation in this area.

## METHOD

A systematic mixed-method approach was adopted, primarily comprising qualitative techniques. The research incorporated 4 stages:

**Phase 1:** Unstructured interviews with doctors and nurses, questionnaires to pharmacists and to prescribers to obtain the viewpoint of practitioners directly engaged in patient care.

**Phase 2:** Semi-structured interviews with policy-makers and experts exploring their perceptions on health care provision, payer advocacy, health economics and pharmaceutical policy.

**Phase 3:** Semi-structured interviews with regulators seeking their perspectives on the impact of pharmaceutical regulation in this field.

**Phase 4:** A focus group was conducted with the aim of consolidating and validating the findings and proposals of the study.

Directed content analysis was used to evaluate and interpret the results. The coding guide was developed through the literature review.

## RESULTS

### Member State Level: Medicines Access

Deterrents to medicines' access are entrenched, and sometimes replicated, at various strata of the health systems of the member states. The advantages that a documented national medicines policy may bring in this context are not fully understood or implemented. The multiplicity of factors impacting access are also over-arching at a pan-European level.

### E.U. Level: Policy

It would be difficult for a pan-European policy targeting access to medicines to accommodate the wide spectrum of divergences between the member states. Additionally the consensus in the member states is that Europeanisation of the pharmaceutical arena should not be further developed at this time.

### Pan-European Potential

The European Union's potential for providing technical support, networking and co-operation, establishing scientific norms, capacity building and the co-ordination and dissemination of information, should be exploited. The current initiative to revise the legislation should strategise access to medicines as a focal point.

## CONCLUSION

Measures to mitigate the challenge of medicines' access are best taken conjointly at European Union level and in the member states. The latter should adopt a transparent, cohesive and documented national policy which explicitly upholds access to medicines, provides clear direction and serves as a platform towards fostering this goal.

To be fit for purpose, such a policy must be participative and inclusive of all actors and must be developed in accordance to each country's needs and resources. The Commission has a role in supporting and complementing the member states by developing generic facilitating frameworks.

## REFERENCES

[1]Michalopoulos S. Pharma Industry Cannot Escape Drug Price Talks. Brussels: 2016.
[2]Report on EU options for improving access to medicines (2016/2057(INI)), available at: http://www.europarl.europa.eu/doceo/document/A-8-2017-0040_EN.html
[3]Verheugen, G. (29/09/2006), Delivering better information, better access and better prices, published by the European Commission, available at: http://europa.eu/rapid/press-release_SPEECH-06-547_en.htm cited: 22nd Oct 2017

- Wismayer, L., Zarb Adami, M., Azzopardi, L.M. 'A Framework facilitating Access to Medicines in the European Union', 27th Annual Congress of the European Association of Hospital Pharmacists. 2023 March 22-24. Lisbon, Portugal.

Citation:

European Journal of Hospital Pharmacy Mar 2023, 30 (Suppl 1) A171-A172; DOI: 10.1136/ejhpharm-2023-eahp.357

http://dx.doi.org/10.1136/ejhpharm-2023-eahp.357

term). We included studies evaluating CSTD, safe handling and drug quality.
**Results** We included 7 articles (one systematic review, four reviews and two prospective studies) that showed the following critical issues:

- There is a wide variety of components in CSTDs that can potentially cause incompatibility issues, physical and chemical instabilities as well as drug loss and poor quality product due to adsorption onto CSTD materials.
- CSTDs are associated with higher incidence of insoluble fine particles related to silicone oil droplets. MAb are known to form aggregates when CSTDs are used that could be potentially detrimental to patient safety.
- CSTDs holdup volume range from 0,04 to 1 mL which has an impact on deliverable drug dose which is especially worrying in low volume-dose IDP.

**Conclusion and Relevance** Frequently, there is insufficient information to exclude safety concerns for IDP leading to broad use of CSTDs according to guidelines.

There is an urgent need to increase knowledge about the hazard of new therapies and to assess CSTDs impact on product quality, clinical trial outcome and patient safety.

**REFERENCES AND/OR ACKNOWLEDGEMENTS**
**Conflict of Interest** No conflict of interest.

## Late breaking abstracts

### 1ISG-003 PROTOCOL FOR THE OPTIMISATION OF PHARMACEUTICAL VALIDATION IN HOSPITALISED PATIENTS

[1]R Claramunt García, [1]M Merino Almazán, [1]T Sánchez Casanueva, [2]N Garcia Gomez*. *[1]Hospital Virgen De Altagracia, Pharmacy, Manzanares, Spain; [2]Hospital Universitario De Jaén, Pharmacy, Jaén, Spain*

10.1136/ejhpharm-2023-eahp.356

**Background and Importance** Pharmacist validation of hospitalised patients' medication is a fundamental task that spends much of the hospital pharmacist's time.
**Aim and Objectives** To establish a protocol for optimisation of pharmaceutical validation through the analysis of the validation timetable of prescribing physicians.
**Material and Methods** A validation statistics report was carried out for the prescribing medical staff for the last 6 months (March 2022 to September 2022). In this, the total validations were divided into the 24 hours of the day, calculating the percent corresponding to each of the hours. With the results obtained, an analysis was made of the hours with the most validations per day. With this, the pharmacist validation was adapted to those hours in such a way that most prescriptions were reviewed shortly after being validated by the doctor, and the rest of time were left for other assistance tasks of the pharmacist.
**Results** The hours with the highest medical validation were 10 a.m. (15.98%) and 11 a.m. (13.52%), while the night hours (0 a.m. to 7 a.m.) had the least validation (0.06–1.03%). Therefore, the pharmaceutical validation schedules were adapted to the following:

- 8 am: to review the treatments validated by the physician between 3 p.m. and 8 a.m. (hours in which the Pharmacy Service is closed), and which correspond to 27.48% of daily medical validations.
- 11 am: to review the treatments accumulated in the hours with the highest medical validation. They correspond to 36.71% of daily medical validations.
- 2 pm: to finish reviewing pending treatments before sending the medication to the patients (which is at 3 p.m). They correspond to 35.81% of daily medical validations.

**Conclusion and Relevance** Optimising the timetable of pharmaceutical validation allows the pharmacist to use the rest of the time in other care tasks, which has a positive impact on patients, while still being able to resolve any discrepancies found in the validation at the right time.

**REFERENCES AND/OR ACKNOWLEDGEMENTS**
**Conflict of Interest** No conflict of interest

### 1ISG-009 A FRAMEWORK FACILITATING ACCESS TO MEDICINES IN THE EUROPEAN UNION

L Wismayer, M Zarb Adami, LM Azzopardi*. *University of Malta, Department of Pharmacy, Msida, Malta*

10.1136/ejhpharm-2023-eahp.357

**Background and Importance** In the European Union (EU), access to medicines is established as a fundamental right, enforceable through the judicial system. However, equity to access has become increasingly challenging, with Member States adopting different healthcare models seeking to attain cost-containment quality of care and improved patient outcomes. As a result, patients experience disparate levels of access to medicines. Ensuring enhanced, timely and equitable access is acknowledged as an important goal. This study sought to identify access enablers which may be embedded in the wider health system domain and flexibly adopted by EU Member States.
**Aim and Objectives** To identify and evaluate factors which impact medicines' access and propose a methodology enabling sound decision-making strategies optimising timely patient access to effective medication.
**Material and Methods** The study consisted of four phases. Phase 1 addressed pharmacists and healthcare professionals, intended to obtain their feedback on access to medicines through unstructured open-ended questionnaires. In phase 2, structured interviews were held with pharmaceutical policymakers and experts. Phase 3 consisted of a questionnaire to pharmaceutical regulators and prescribers. In Phase 4, a focus group discussion was organised with policymakers and regulators to collate qualitative and quantitative data and propose the factors impacting medicines access and obtain consensus on the developed access framework.
**Results** The developed access framework consists of four dimensions that highlight indicators supporting strategies to optimise timely patient access to medication. The domains and the respective indicators are: 1) Uptake (reimbursement, affordability, sustainability); 2) Utilisation (shortages, rational use through protocols, educational material); 3) Audit

(utilisation studies, prescribing databases and patient registers); and 4) Re-evaluation (re-appraisal, actioning of audit results).
**Conclusion and Relevance** The developed access framework can be implemented across different healthcare ecosystems and in different EU countries to identify strategies and actions that improve timely patient access to good quality, safe and effective medicines. A structured generic framework that provides a common decision-making platform, but which may be flexibly adopted by the Member States offers an opportunity to strengthen the effectiveness and resilience of European health systems and provide improved patient care. Access to effective medication is a multi-faceted issue which, unless appropriately understood and managed, has the potential for grave repercussions to public health.
**Conflict of Interest** No conflict of interest

## 1ISG-010 PHARMACY STAFF SATISFACTION AND OPINION OF NEW WEBSITE APPLICATION FOR OUTPATIENT CARE

A Merino*, N Herrero Muñoz, AB Fernández Román, B Hernández Muniesa, A Pou Alonso, A Ontañón Nasarre, J Pedreira Bouzas, MJ Canalejo Fuentes, M García Gil. *Hospital Universitario De Fuenlabrada, Servicio De Farmacia, Madrid, Spain*

10.1136/ejhpharm-2023-eahp.358

**Background and Importance** Up until March 2022, medical prescription orders and next appointments were printed on paper for pharmaceutical validation and medication dispensation. A new website was developed to optimise this process.
**Aim and Objectives** Assess the level of improvement and satisfaction of professionals with the new outpatient website application.
**Material and Methods** A seven question Likert-type survey was conducted in September 2022 among pharmacy technicians and pharmacists who had worked with and without the new website. There were five questions assessing patient waiting time, time spent on pharmaceutical validation and dispensation, communication between pharmacists and technicians, safety, and information accessibility about patients and their treatment. There were two remaining questions assessing global satisfaction before and after the web. To assess improvement and satisfaction, answers were scored from one (totally disagree) to five (totally agree). All questionnaires were anonymous. The mean score was calculated with Microsoft Excel® (v.2019) for each of the questions. The results obtained were analysed for each of the professional categories.
**Results** A total of 14 pharmacy technicians and 17 pharmacists were included. According to technicians, 40% (6) believe that patient waiting time has been reduced (mean: 3), 27% (4) believe that validation and dispensing times have been reduced (mean: 3), and 20% (3) believe that technician-pharmacist communication has improved (mean: 3). 80% (12) answered that safety has improved (mean: 4) and 47% (7%) responded that accessibility to information regarding patients and their treatment has improved (mean: 3). 76% (13) of pharmacists responded that patient waiting time has been reduced (mean: 4), 82% (14) thought that the time spent on validation and dispensation has been reduced and that technician-pharmacist communication has improved (mean: 4). 88% (15) believe that safety has improved (mean: 4) and 100% (17) of pharmacists believe that accessibility to information regarding patients and their treatment has improved (mean: 5). The global average satisfaction without the website was 3 points, with the website was 4 points for technicians and 5 points for pharmacists.
**Conclusion and Relevance** Staff opinions differ according to their professional category: for pharmacists, the new web has reduced working time and has improved communication, safety and accessibility to treatment. For technicians, it has only improved safety. However, the overall staff satisfaction with the website is higher.

### REFERENCES AND/OR ACKNOWLEDGEMENTS

**Conflict of Interest** No conflict of interest

## 1ISG-011 MANAGEMENT OF UNADMINISTERED THERAPIES: IMPACT OF PHARMACIST-DOCTOR COLLABORATION TO OPTIMISE THE PROCESS OF PREPARING CANCER THERAPIES

[1]S Giorgetti*, [2]C Cardinali, [1]A Morichetta, [1]C Antolini Broccoli, [1]J Montecchia, [1]A Minnucci, [1]L Fazi, [2]C Polidori, [1]L Scoccia. *[1]AV3 Asur Marche Macerata, Uoc Farmacia Ospedaliera Macerata, Macerata, Italy; [2]University of Camerino, School of Hospital Pharmacy, Camerino, Italy*

10.1136/ejhpharm-2023-eahp.359

**Background and Importance** At our Antiblastic Drugs Unit (ADU), pharmacy staff fulfil requests from three hospitals. From October 2021 to March 2022, oncological preparations were frequently returned unused. In some cases, the preparations could be reused, but many others were disposed of. In order to reduce waste and improve efficiency, the costs were quantified in terms of economic value as dedicated time and sharing results with prescribers.
**Aim and Objectives** This work evaluated how pharmacist-doctor collaboration could reduce waste and optimise the process of setting up oncological therapies
**Material and Methods** An Excel file recorded the returns, quantified the cost of the therapies disposed of and the therapies recovered before and after the collaboration with prescribers, with whom it was agreed to give double confirmation before setting up therapies that are costly and/or have short chemical-physical stability.
**Results** Between 1 October 2021 and 31 March 2022, out of 13,008 therapies set up, 210 (1.6%) were returned, for an economic value of € 96,192. Of these, 141 (67.14%) were reassigned to other patients and thus € 58,926 were recovered, but 69 of them (32.86%) were disposed of, thus wasting € 37,266. The time dedicated by the ADU staff was 28 hours (8 minutes for each preparation). After implementing a collaboration with clinicians (April to May 2022) only 43 therapies were returned, on average 21.5 per month for an economic value of € 18,661. Of these, 33 (76.7%) were reused, recovering € 12,989 and 10 of them (23.25%) were disposed of, wasting € 5,672.
**Conclusion and Relevance** Hospital pharmacists tracked cancelled therapies and communicated these findings to prescribing physicians. By implementing corrective measures, this collaboration proved successful in optimising the use of resources and for further improvement of traceability, a special return form will be made.

L-Università ta' Malta
Faculty of Medicine & Surgery
Department of Pharmacy

# A FRAMEWORK FACILITATING ACCESS TO MEDICINES IN THE EUROPEAN UNION

L. Wismayer[1], M. Zarb Adami[1], L. M. Azzopardi[1]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

Contact: lilwism@gmail.com

1ISG-009

## BACKGROUND AND IMPORTANCE

In the European Union, access to medicines is established as a fundamental right, enforceable through the judicial system. However, equity to access has become increasingly challenging, with Member States adopting different healthcare models seeking to attain cost-containment quality of care and improved patient outcomes. As a result, patients experience disparate levels of access to medicines. Ensuring enhanced, timely and equitable access is acknowledged as an important goal. This study sought to identify access enablers which may be embedded in the wider health system domain and flexibly adopted by EU Member States.

## AIM

To identify and evaluate factors which impact medicines' access and propose a methodology enabling sound decision-making strategies optimising timely patient access to effective medication.

## METHOD

The study consisted of four phases:

**PHASE 1**

Addressed pharmacists and healthcare professionals and was intended to obtain their feedback on access to medicines through unstructured open-ended questionnaire.

**PHASE 2**

Structured interviews were held with pharmaceutical policy makers and experts.

**PHASE 3**

Consisted of a questionnaire addressed to pharmaceutical regulators and prescribers

**PHASE 4**

A focus group discussion was organised with policy makers and regulators to collate qualitative and quantitative data and propose the factors impacting medicines access and obtain consensus on the developed access framework.

## RESULTS

The developed access framework consists of four dimensions that highlight indicators which support strategies to optimise timely patient access to medication:

| DOMAIN | INDICATORS |
|---|---|
| Uptake | • Reimbursement<br>• Affordability<br>• Sustainability |
| Utilisation | • Shortages<br>• Rational use through protocols<br>• Educational material |
| Audit | • Utilisation studies<br>• Prescribing databases<br>• Patient registers |
| Re-Evaluation | • Re-appraisal<br>• Actioning of audit results |

## CONCLUSION

The developed access framework can be implemented across different healthcare ecosystems and in different EU countries to identify strategies and actions that improve timely patient access to good quality, safe and effective medicines.

A structured generic framework that provides a common decision-making platform, but which may be flexibly adopted by the Member States offers an opportunity to strengthen the effectiveness and resilience of European health systems and provide improved patient care.

Access to effective medication is a multi-faceted issue which, unless appropriately understood and managed, has the potential for grave repercussions to public health.

## REFERENCES

[1]Michalopoulos S. Pharma Industry Cannot Escape Drug Price Talks. Brussels: 2016.
[2]Report on EU options for improving access to medicines (2016/2057(INI)), available at: http://www.europarl.europa.eu/doceo/document/A-8-2017-0040_EN.html
[3]Verheugen, G. (29/09/2006), Delivering better information, better access and better prices, published by the European Commission, available at: http://europa.eu/rapid/press-release_SPEECH-06-547_en.htm cited: 22nd Oct 2017

**Intended Publications:**

- Title: Access to Medicines: The impact of policy and regulation in the European Union.

  *Intended Journal: Research in Social and Administrative Pharmacy*.

  Stage: Writing-Up

- Title: Empowering Health Care Professionals to Optimise the Rational Use of Medicines.

  *Intended Journal: Journal of Pharmacy Practice and Research.*

  Stage: Planning

- Title: Medicines' Inequities in the European Union: A conceptual framework for improvement.

  *Intended Journal: British Journal of Medical and Health Research.*

  Stage: Planning