The path from clinical evidence to use of drugs
Marketing analysis of factors influencing the market performance of drug therapies

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1. Introduction

Over the past two decades, the annual turnover of the global pharmaceutical market has grown from $390 billion to about $1.27 trillion, according to recent estimates. Hundreds of pharmaceutical companies and research laboratories and countless academic and other institutions have been working to find better and better solutions to unmet medical needs.

The subject of my doctoral research was formulated many years ago: namely, as whether patients—at a macro level, and at the end of a complex drug-prescribing process—can obtain access to clinically more beneficial therapy involving active ingredients (APIs) that result from pharmaceutical innovation.

Personal inspiration may be a major determinant of the success of any research project. As it may be of great help for understanding the research dilemma and the doctoral thesis, I would like to briefly discuss my inspiration in the introduction. In addition to my studies in economics, as a student of pharmaceutical chemical engineering I had to achieve an in-depth understanding of how API molecules are constructed and how their synthesis is achieved. Throughout my studies, it became clear to me that the very essence of medicine and pharmaceutical research is to generate appropriate pharmacological responses to unmet medical needs. The route to effective pharmacological solutions leads through research into mechanisms of action. By discovering the right mechanisms of action and intervention, researchers enable the restoration or maintenance of the desired health status as far as this is possible. Pharmaceutical research is carried out in line with these classes of mechanisms of action, the outcome of which is the production of active ingredients. Multiple mechanisms of action and multiple APIs within these classes are generated in response to unmet needs, as shown in Figure 1. With an accurate understanding of such syntheses, it has become apparent that while the chemical structures of drug molecules differ between classes of mechanism of action, within the same class of mechanism of action the chemical structure of APIs is very similar, with individual APIs typically differing only in minor details.

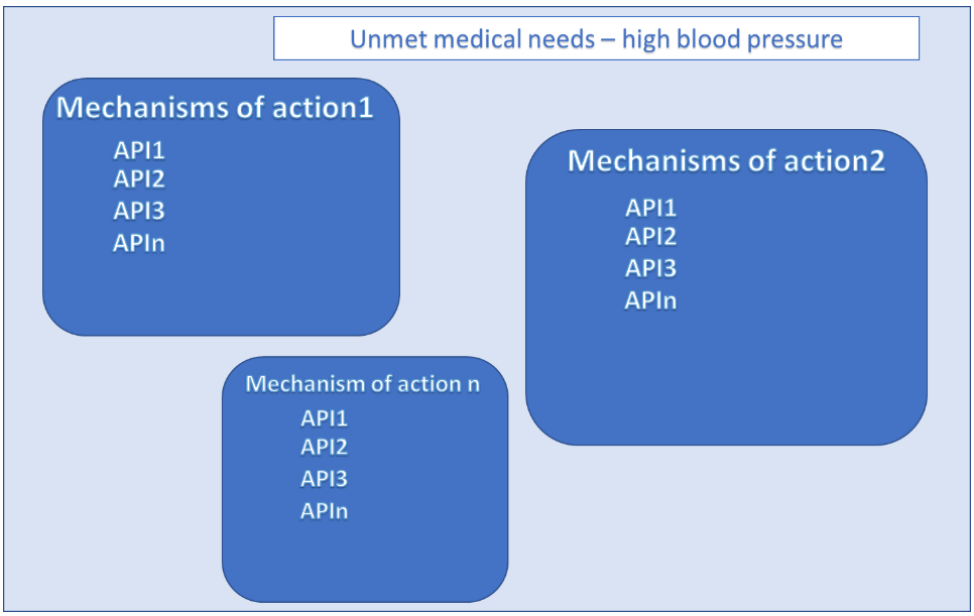


Figure 1 Schematic diagram of the relationship between unmet medical needs and mechanisms of action in response to these needs and APIs

Therefore, from a marketing point of view, pharmaceutical research offers genuinely different solutions to meet needs at the level of mechanism of action, while within mechanisms of action it seeks to optimize product attributes. Since the latter products are substitutes, it is reasonable to ask whether consumers are getting the best possible alternative from an often very wide range of APIs. The question also arises as to whether pharmaceutical innovations always lead to real benefits in terms of products, or whether parallel innovations—when unmet medical needs linked to considerable business interests—lead to discovery of very similar therapeutic solutions. The central task of my thesis is exploring how the market performance of substitutable and often indistinguishable APIs is affected by the clinical appropriateness of the products. By exploring the complexity of the drug-purchasing process, I also attempted to investigate what other factors can influence the market performance of active ingredients.

1.1. Theoretical and practical relevance of the research

The pharmaceutical industry, which generates well over $1.2 trillion in revenue, has one real goal beyond making corporate profit, and that is improving the health of patients at a societal level. This goal can be achieved by creating effective drugs with an appropriate side-effect profile – that is, which are as safe as possible. Due to the complexity of the industry, most pharmaceutical research questions can only be addressed in a multidisciplinary context. This is also true when relationships are investigated, and the question is whether this key product attribute is reflected in the market performance of

clinically preferred APIs. This question can also be considered from the perspectives of medicine, pharmacy, health economics, pharmaceutical policy, macro- and microeconomics, and marketing. The issue can be tackled descriptively and analytically, cross-sectionally or longitudinally, and also on a single-country or multi-country sample. The literature review, research findings, and my professional experience have led me to believe that the basic issue can only be adequately addressed in a cross-disciplinary setting and that, due to the specificities of the pharmaceutical industry, a longitudinal analysis of market performance cannot be avoided if one seeks to understand the trends. It can also be argued that, due to the general nature of the research question, it is necessary to analyse a sample of a larger group of countries, as single country samples cannot explain macro-level relationships and may lead to false conclusions. In this doctoral research, my aim is to explore this complexity and propose a framework for a general investigation of the central research dilemma. I believe that the novelty of this approach, both from a practical and theoretical point of view, lies in the synthesis of the factors listed above.

1.2. Research framework in the context of the pharmaceutical industry

The complexity of the research question is to be found in the particularly complex context of the studied pharmaceutical industry. In the pharmaceutical market, the prescribing physician has the greatest decision-making potential when it comes to the purchasing decision, along with the patient, who is the final consumer. In addition, the health care system that finances the therapy cannot be ignored, not to mention the intertwining of regulations, corporate interests and positions, and their effects. The following factors should be considered while investigating the research question:

- The clinical appropriateness of an active ingredient as a key product attribute in relation to different mechanisms of action. Clinical preferences can only be assessed on the basis of sufficient and reliable evidence. The study of this issue is a distinct discipline, and multidisciplinary in itself.
- The industrial property framework, with particular emphasis on patents. It is essential to clarify whether research is carried out in a monopolistic market for original molecules, or in a generic market for off-patent drugs, or a mixture of both, which is the characteristic of the period under study. As patent protection has both spatial and temporal limits that can vary from country to country, this aspect must be clarified. The issue is further complicated by the fact that, in

addition to so-called basic patents, market competition is enhanced by the existence of additional patents for selection, formulation, indication, etc., thus potentially expanding the market presence of a monopoly.

- Timing of innovation, diffusion of innovation. Again, when this factor is explored, a diffuse picture emerges, both in terms of time and space.
- Level of product definition in the competitive analysis (here, level of APIs, or level of brands). As regards innovative therapies, competition remains at the level of APIs during the patent protection period (competition between needs groups). During this period innovative brands and APIs are the same in terms of market performance. As patents expire, APIs become generic, giving the opportunity to other pharmaceutical companies in addition to the originator company to market pharmaceutical products based on the same API with the same quality and pharmacokinetic properties. Thus, following the patent expiry, the number of brands of each API increases and market concentration decreases proportionally.
- Pharmaceutical policy instruments. Despite harmonization efforts, this is also an issue that varies from country to country, involves a myriad of instruments, and is a major focus for each country due to the need to optimize the allocation of scarce resources. Particularly relevant to research are marketing authorization, resource generation and drug financing, drug pricing, the reimbursement system, and the development of principles for official authorization.
- Prescription (Rx) or OTC (over-the-counter) drug therapies. For Rx products, prescribing is of central importance, while the regulation of marketing communication, availability of drugs, pricing and reimbursement are key factors. These are considered more stable in terms of time compared to the previous factors, but changes in prescription status can occur and examples of variation between countries can also be found.
- Impact of marketing factors, and the activities of pharmaceutical industry players. Considering the previous factors (originator/generic; Rx/OTC; clinical evidence), it is necessary to investigate the marketing efforts of sales-interested pharmaceutical players.
- The (role of the) perceptions of physicians, which is one of the key factors associated with Rx products, is the outcome of the above factors.

By defining the framework, my initial assumption is that the clinical appropriateness of drugs should impact its market performance. Clinical appropriateness is a universal concept that can be defined in the context of available clinical evidence.

For reasons of comparability, *I define the depth of the investigation at the level of APIs.* I do this because this is the level at which it makes sense to distinguish between drugs on a scientific basis. (My assumption is that, due to the concept of generics, the rigour of authorization for products with the same API ensures the same quality.) Aggregate sales volumes of APIs can thus provide a good basis for comparison between different drug therapies. I consider it an important condition that my research is carried out in relation to *the market for generic APIs.* Since the monopolistic market for patented APIs deserves separate consideration. I will include APIs for which the *restrictive patent expired at least five years ago.* This may be critical in the sense that the effects of regulatory and competitive conditions can lead to balanced market conditions throughout this period. This process is meant to lead to the emergence of generic competitors and market reallocation. It is also a necessary condition that *no innovative therapy has emerged for the given indication,* or this would have redefined the whole market. The analysis is carried out *on the market for prescription-only APIs.* In the prescription-only market, physicians act as patients' agents, and consumers and decision-makers are clearly separated in the purchasing process. Assuming professionally responsible prescribing processes, the main motivation of physicians should be to select a clinically appropriate therapy. Having said that, due to the inescapable control of physicians I would assume a greater impact clinical evidencein the Rx market than in the OTC market. A further argument in favour of examining the Rx market is that the impact of advertising targeted at final consumers can be ignored due to the rigour associated with pharmaceutical advertising (Gönül et al., 2001).

My hypothesis is that, in the long term and under good competitive conditions, the positive attributes of clinically more effective and safer APIs should be reflected in the sales of drugs. This may be distorted by country-specific price levels, pharmaceutical policy instruments, the marketing efforts of manufacturers, and the interplay between these factors. The doctoral research will seek to reveal identifiable patterns by looking at the European pharmaceutical market at a systemic level.

Within the outlined framework, my theory suggests that clinical appropriateness is reflected in the market sales of APIs in the following ways. After the expiry of patent protection, generic manufacturers tend to favour drug therapies that are best suited to

convincing prescribing physicians. The clinical appropriateness of the APIs is critical to persuading physicians – an effect which is further reinforced by professional guidelines. To avoid encountering a competitive disadvantage, generic manufacturers develop and market the clinically most appropriate therapy and allocate marketing expenditure to this area, thereby increasing the level of information in the market. Since the analysis is done at the level of APIs and not at the level of manufacturers' brands, generic competition should enable a clinically preferable API to achieve higher sales volumes. At the same time, clinically less advantageous therapies will increasingly be squeezed out of competition.

1.3. Field of research: drug therapies

For the analysis, I was required to select an indication class that meets the criteria of the outlined framework. Accordingly, hypertension drug therapies were selected:

- Several drug classes for treating hypertension are distinguished based on their mechanism of action (diuretics, ACE inhibitors, ARBs, etc.).
- Within each drug class, a number of drug therapies are considered (e.g., more than ten ACE inhibitors and eight ARBs) due to the importance and duration of research in this area.
- Within the two classes, the patent expiry of APIs is well above the limit.
- APIs are prescription-only drugs and are available in the studied countries.

The basic concept was to prioritize hypertension drug therapies according to mechanism of action at the inter-class level, and also at the intra-class level of individual APIs. However, following consultation with physicians, I included only two classes and their APIs in the analysis. These were the classes of angiotensin-converting enzyme (ACE) inhibitors (ATC code C9A) and the class of angiotensin II receptor antagonists (ARBs) (ATC code C9C). The reason for this screening was that therapies with different mechanisms of action are used to treat diseases other than hypertension. As they also appear in the aggregate sales data, I would not have been able to ensure comparability. These two classes meet all the criteria, as they are predominantly prescribed for the same indication. No similar exclusion was necessary between the APIs at intra-class level.

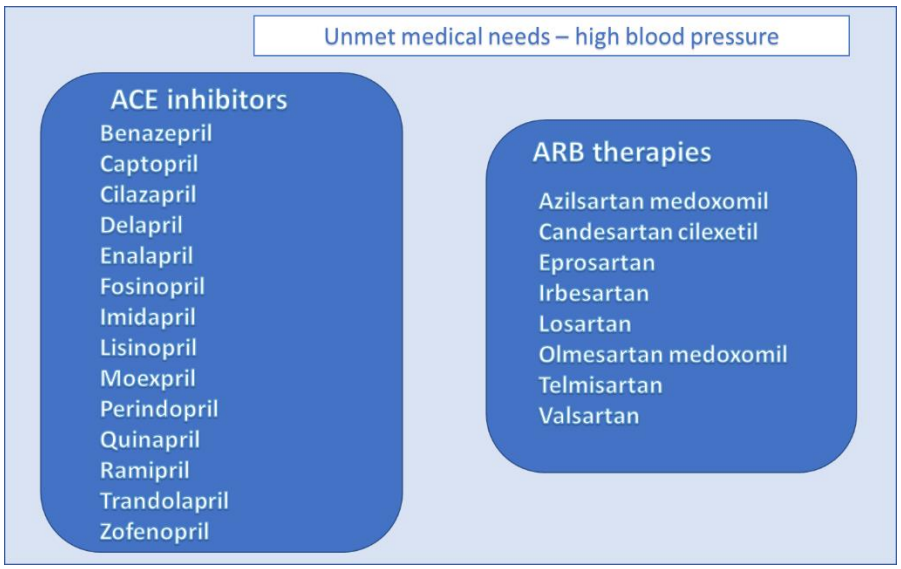


Figure 2 Field of research: drug therapies

2. Literature review

2.1. The pharmaceutical market and its players

2.1.1. The market

Human rights to health include the right of access to essential, quality-assured healthcare technologies, including medicines (Hogerzeil, 2006). Essential medicines can meet the priority health needs of a population. For this reason, it is important that, in functioning healthcare systems, essential medicines are always available in adequate quantities, in appropriate dosage forms, at a guaranteed quality, and at prices that individuals and communities can afford (Quick et al., 2002).

Since health is one of the most important factors in the life of each and every individual, they are willing to spend money to maintain and protect health and prevent its deterioration. How much the citizens of a country will spend on health-related expenditures varies widely from country to country, even among countries in the European region (Nolte-Corbett, 2015, Nolte et al., 2011, Ferech et al., 2006). Among the determinants, the market entry of competing medicines (Godman et al., 2013), changes in clinical guidelines and adherence to them, different cultural attitudes and beliefs about medicines, and pharmaceutical policy instruments are to be emphasized.

Obviously, the market performance of drugs will not only be determined by their clinical appropriateness. On the one hand, full information cannot be achieved within the system.

This may be due, inter alia, to the distorting influence of lay people, people with different levels of information, corporate and political interests, and the complex nature of the assessment. On the other hand, decisions about particular drugs are not solely based on their scientific ranking. The price of the therapy, the availability of products, and, of course, marketing communication about products have a strong influence. Therefore, picking one element of the marketing mix and interpreting its impact cannot serve to evaluate the overall sales process or market performance. However, to build a well-defined theory, this is what I do in my research (Sutton-Staw, 1995; Weick, 1995).

2.1.1.1. Health expenditure trends around the world

In the United States, the world leader for health expenditure, 16.9% of GDP was spent on health, a total of $3,480 billion, equivalent to $10,624 per capita in 2018. However, the US has the lowest share of out-of-pocket expenditure (10.8%), next to France (9.2%). In the European Union, Germany accounts for the highest health expenditure, with €453 billion spent in 2018, 11.4% of German GDP, as shown in Table 1. According to OECD data, 14.4% of this amount was spent on pharmaceuticals, while in Hungary pharmaceuticals accounted for more than 30% of total health expenditure, and 7.1% of GDP (OECD Data, 2017b). These figures do not only indicate the significant economic impact of physicians' choices—and to some extent, those of patients—, but also confirm that there can be significant differences in health expenditure between countries. It is important for both financiers and other pharmaceutical players —who generate more than $1,000 billion in sales globally—to understand physicians' prescribing habits, the influencing factors, and the regional characteristics thereof (Global life sciences sector outlook, 2017).

Table 1 Trends in healthcare expenditure in nine countries and in the USA, 2018 (World Bank Data, 2020)

Country	Total health expenditure (bn USD)	Health expenditure as of % GDP	Per capita health expenditure (USD)	Out-of-pocket financing as a proportion of total health expenditure (%)
US	3480	16.9%	10624	10.8%
DE	453	11.4%	5472	12.6%
NL	91	10.0%	5307	10.8%
FR	314	11.3%	4690	9.2%
UK	286	10.0%	4315	16.7%
IT	181	8.7%	2989	23.5%
ES	128	9.0%	2736	22.2%
HU	11	6.7%	1082	26.9%
PL	37	6.3%	979	20.8%
RO	13	5.6%	687	19.5%

Differences are significant not only in terms of total health expenditure, but also the amount spent on pharmaceuticals. The US, with the highest per-capita drug expenditure ($1,229), and in Europe, Switzerland ($894) and Germany ($884), are on the top of the list, while Canada ($879) and Japan ($803) occupy fourth and fifth place. Russia ($310) and Denmark ($339) have the lowest per capita expenditure. The share of expenses attributable to drugs as a proportion of total health expenditure tends to be higher in lower-income countries. See Figure 3.

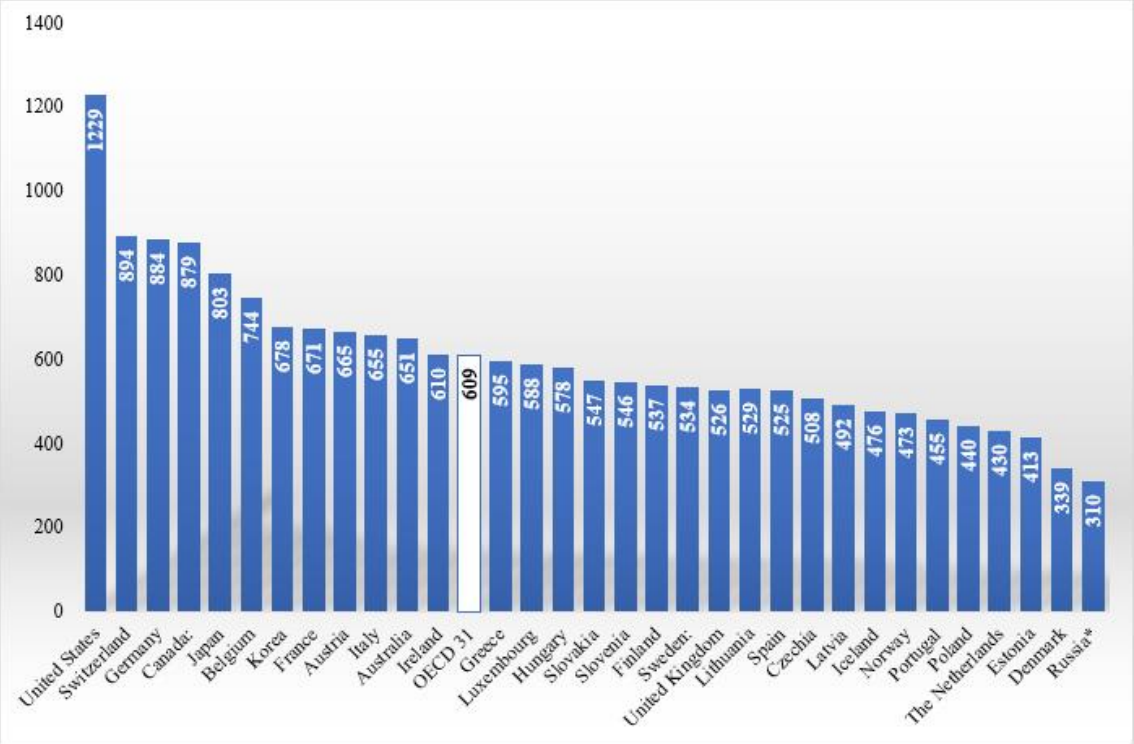


Figure 3 Total drug-related expenditure per capita (USD PPP), 2020 (Source: OECD Health Statistics [database], 2020)

The share of pharmaceutical expenditure in total health expenditure also varies widely: while in Hungary (26.9%), Latvia (26.5%), Greece (26.2%) and Slovakia (25.5%) more than a quarter of health expenditure goes on pharmaceuticals, this share is less than a tenth in the Netherlands (7.5%), Norway (7.1%), and Denmark (6.4%).

In the OECD countries, about 15% of health expenditure is accounted for by pharmaceuticals, and in general, pharmaceutical expenditure is increasing, although at a slower pace, and drug sales have primarily increased in hospitals rather than in pharmacies. This growth has been driven by several parallel processes. With an ageing population and the prevalence of chronic diseases, drug consumption is also growing (OECD, 2017a; Belloni et al., 2016). See Figure 4.

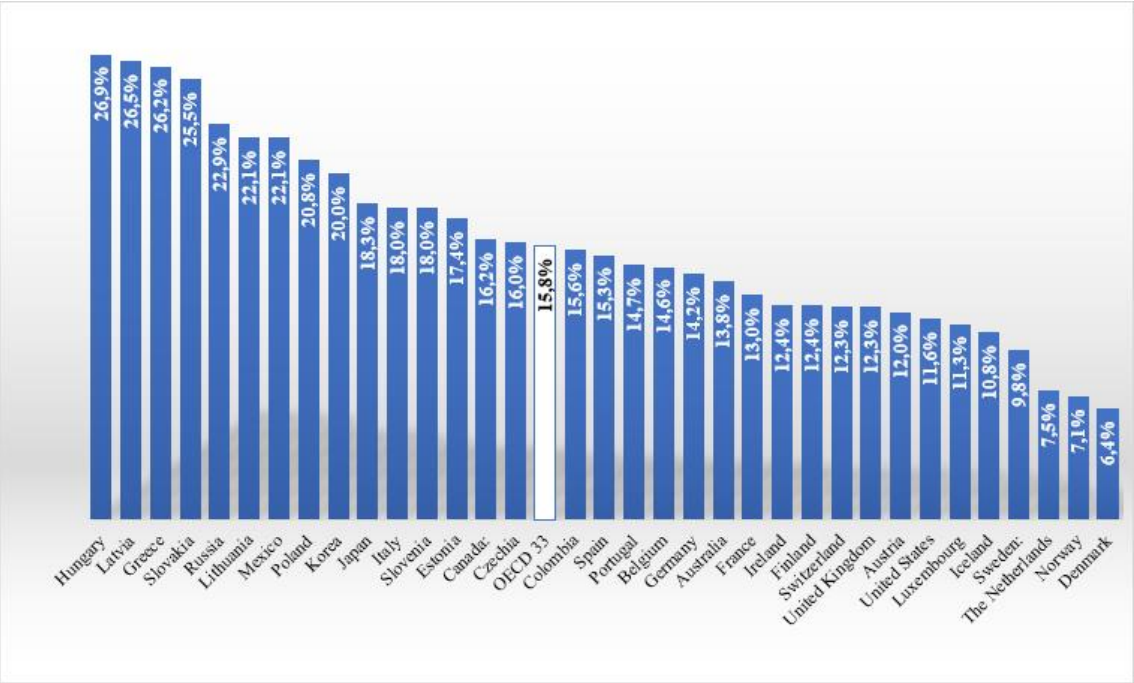


Figure 4 Retail drug expenditure as a share of total healthcare spending, 2018 (Source: OECD Health Statistics [database], 2020)

2.1.1.2. Sales trends of antihypertensive drugs

Additional to the general trends, it is important to investigate macro-level trends in the sales of APIs for hypertension drug therapies since these are the focus of the present PhD research. Throughout the entire period under investigation, the sales volume of ARBs and ACE inhibitors increased in all countries (Figure 5). However, while in Germany, Poland, the United Kingdom and Hungary ACE inhibitor sales plateaued or declined slightly in recent years, ARB sales increased, but in France the two classes of drugs moved in just the opposite direction. France is the only country in which ARB sales exceeded (after 2005) the sales of ACE inhibitors. For the three Eastern European countries, ARB sales started to increase only from the late 2000s onwards, as opposed to in Western countries. At about the same time as ARB sales in the Eastern countries increased, in France the increase in the sale of ARBs stopped abruptly and remained essentially stable for almost ten years.

A comparative analysis reveals that the turnover of single-ingredient formulations was higher than that of combination drugs in all but a few countries. In France, for a short period in the early 2000s, and in Germany from 2012–2013 onwards, sales of combination ARBs were equal to or slightly higher than sales of single-ingredient ARBs. In Hungary, for ACE inhibitors, sales of single-ingredient ACE inhibitors steadily declined from 2006

onwards, accompanied by an increase in sales of combination drugs, resulting in almost equal sales of the two classes by the end of the period under review.

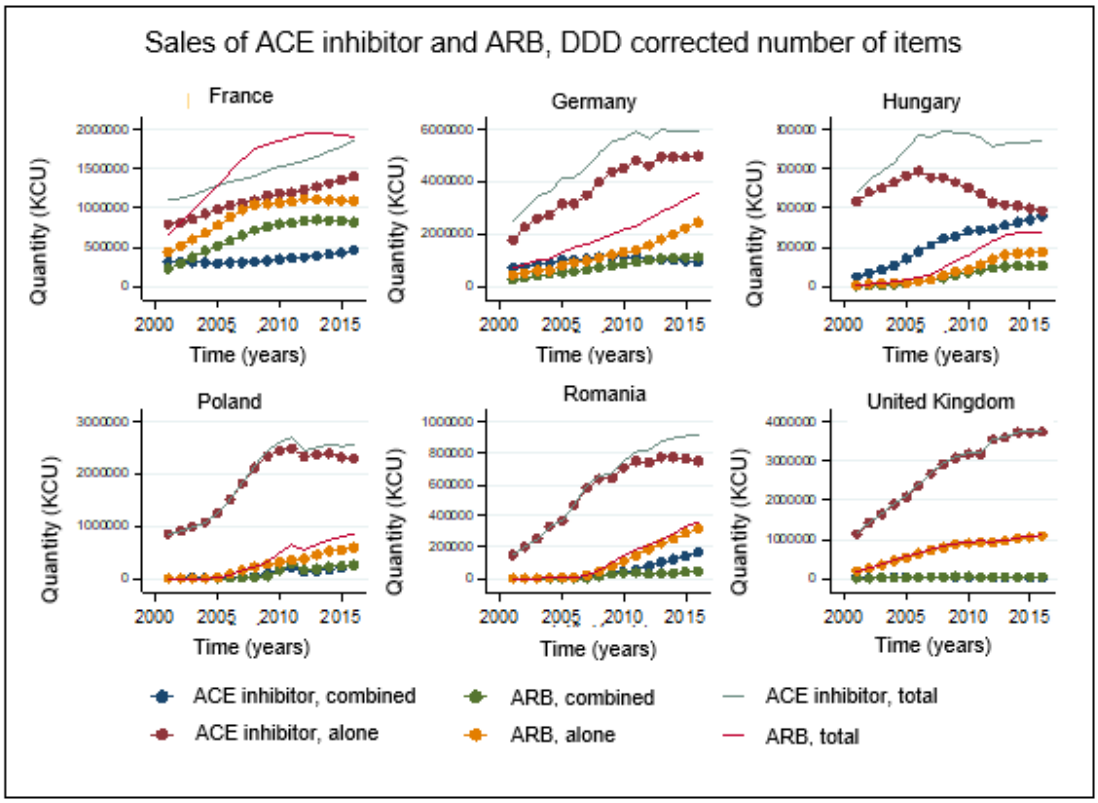


Figure 5 Trends in DDD-adjusted sales volume of ARBs and ACE inhibitors, 2001–2016 (author's editing)

2.1.1.3. Differences among countries by type of financing

Public pharmaceutical expenditure and policies are embedded in an organizational environment that has the aim of achieving full health coverage (WHO, 2018). Retail pharmaceutical financing can be divided into three groups: public financing, patients' out-of-pocket financing, and financing by voluntary health insurers. The first two categories account for the largest share of funding in OECD countries, albeit with different shares in different countries. The highest share of public financing is found in Germany (82%), France (81%), and Colombia (80%). In terms of out-of-pocket financing, Iceland (58%), Poland (63%), and Latvia (61%) are in the lead. Financing through voluntary health insurance is relatively rare around the world, with only single-digit proportions when it occurs in a country, with two exceptions associated with OECD countries: Canada (31%), and Slovenia (26%), where it accounts for more than a quarter of total financing. See Figure 6.

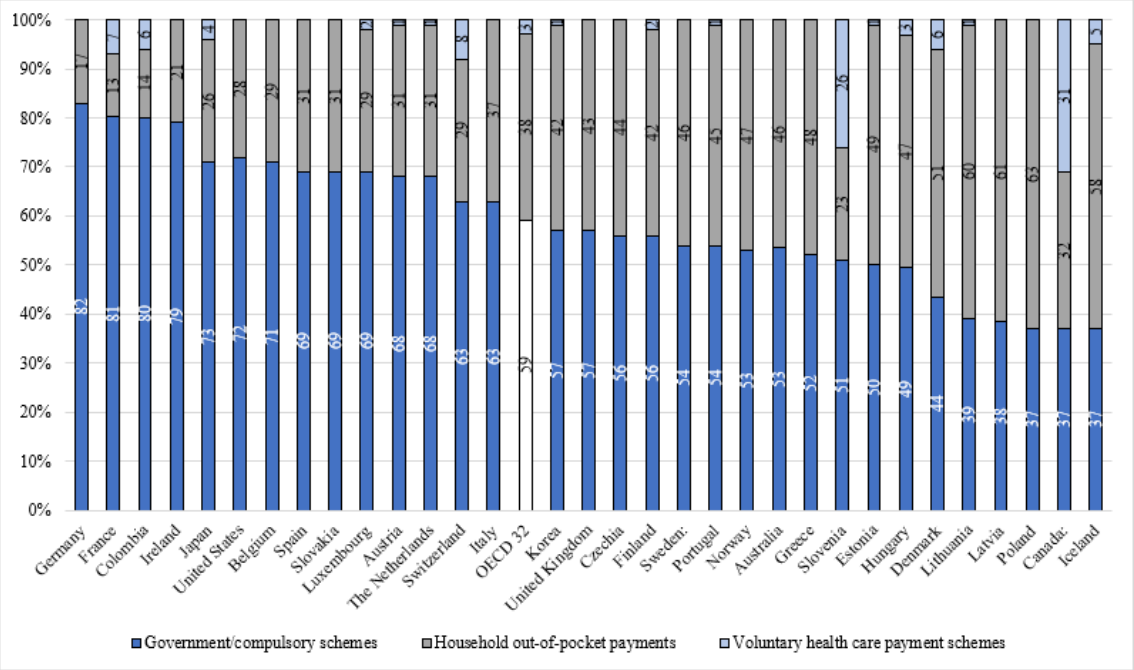


Figure 6 Distribution of retail drug expenditure by type of financing, 2018 (Source: OECD Health Statistics; 2020)

A similar pattern to the previously described trends—depending on the economic situation of the country—can be observed for the distribution of funding sources.

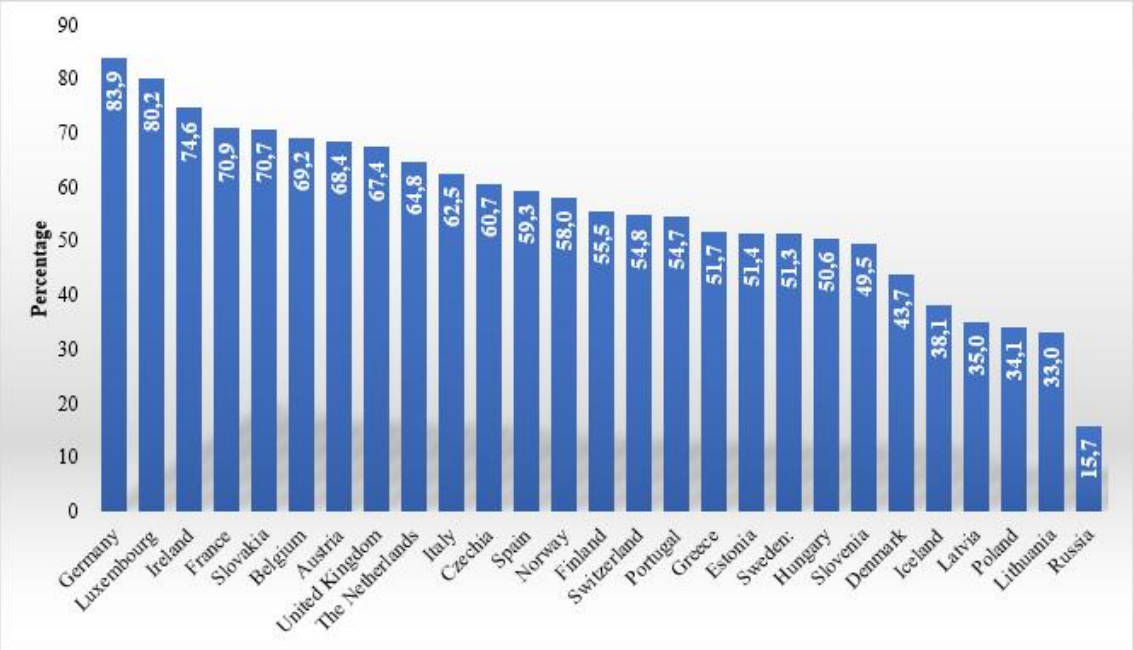


Figure 7 Public pharmaceutical expenditure as a share of total pharmaceutical expenditure in the European countries of OECD, 2015 (Source OECD, 2017b)

Higher-income countries tend to be associated with a greater share of public spending on pharmaceuticals, but not always, ranging from over 80% in Germany and Luxembourg

to 16% in Russia. Nevertheless, healthcare—including pharmaceutical care—is high in many European countries compared to other regions of the world as Figure 7 shows.

2.1.2. Buying-side Actors

Patients appear as primary consumers, but they are not the decision makers in relation to the use of the product; this decision is delegated to special representatives—i.e., physicians or pharmacists, depending on legal restrictions. Thus, physicians become the most important direct customers of pharmaceutical companies in the prescription drug market. On the demand side, physicians act as 'agents', i.e., they review the therapeutic options in the patients' interest, and prescribing becomes the decisive factor in the drug purchasing process. Another feature of the prescription drugs market is that it is not the prescribing doctor, and often not the patient, who pays for the drugs. As with most health services, in a significant number of cases, drug costs are covered—in whole or in part—by a third party such as a private or a public insurer, thus insurers are powerful players in the consumer structure, with the potential to significantly change market conditions (Rácz-Kummer, 2019; Lantos et al. 2006).

Patients are supplied with medicines either by pharmacies through wholesalers or by hospitals. In the EU, hospitals usually purchase drugs directly from manufacturers rather than from wholesalers, but roughly three times as much of the revenue of manufacturers is generated from retail pharmacy sales than from hospital sales (European Commission, 2009).

The sole aim of patients taking drugs is their cure through the most effective therapy with the least side effects. The primary interest of prescribing physicians, by virtue of their profession, cannot be other than that of their patients'. In theory, the responsibility of the financier is more complex. According to the given indication the financier must choose the optimal cost-benefit ratio for the proposed therapy (Bootman-Townsend, 1991).

Nevertheless, literature suggests that physicians play a central role in the prescribing process. Physicians acquire a wealth of information about the clinical appropriateness of drugs through their studies and further training programmes, during drug detailing, and attending symposia (Gönül et al., 2001).

2.1.3. Products

According to the Hungarian Act on Medicinal Products, a medicinal product is defined as 'any substance or mixture of substances presented as a product to be used for the

prevention or treatment of human diseases, or substances or mixtures of substances which, by inducing pharmacological, immunological or metabolic effects, may be used in or on the human body to restore, improve or modify a physiological function of the human body or to establish a medical diagnosis' (Act XCV of 2005). The developing, manufacturing, and marketing of drugs are strictly regulated and controlled in most parts of the world.

The purpose of a medicine as defined (for the prevention or treatment of human diseases) can be achieved by using medicines that are as effective and as safe as possible. Drug efficacy is defined as meaning to what extent a drug can decrease the likelihood of an adverse clinical outcome. Regarding drug safety, the main question concerns what secondary (and usually negative) effects a drug exerts on the human body. Clinical appropriateness is determined by the two effects together. My assumption—and a central thesis of my research—is that different drug therapies are ranked according to clinical appropriateness. This assertion means that I use the fundamental principles of evidence-based medicine in my analysis (Friedland, 1998; Botz, 2014, Hamer-Collinson, 2014), which will be presented in detail in a forthcoming chapter.

In an article, Borjádi and Juhász point out that 'medicine is not an object of desire, [unlike] most consumer goods, but [involves] a real need' (Borjádi-Juhász, 2003). In the drug-prescribing process, this statement can be interpreted to mean that the financier should choose the optimal cost-benefit ratio associated with the proposed therapy in accordance with the given indication (Bootman-Townsend, 1991). Obviously, this assessment should include the benefits, which—when therapies are compared—are in line with the principles of evidence-based medicine, so that the financier must also consider which therapy has been proven to be the best on a scientific basis.

Drugs can also be seen as a special commodity in other respects. The possibility of a variety of forms of market failure (i.e., information asymmetry, mechanisms for reducing competition, externalities) and equity considerations also highlight the role of public regulators (Rácz-Kummer, 2009). As regards medical decisions about product choice, it should also be borne in mind that the drug prescription process does not generally involve entirely free choice, even when professional therapeutic guidelines are followed. The range of drugs that can be prescribed is usually limited by the accessibility of a particular therapy. Some drugs may not be marketed by the manufacturer in a particular country, or may not be authorized by a local pharmaceutical authority. Even if a drug is available, access may be severely limited by its high price or the level of reimbursement of health

insurance and the costs borne by the patient. In other words, physicians' prescribing options and patients' preferences are limited by various factors associated with the pharmaceutical market. The interplay between these factors is made even more complex by pharmaceutical manufacturers' marketing activities: this involves competing firms, brands, and products (Mamdani et al., 2008; Zwolsman et al., 2012).

Considering product definitions in the context of innovation in the pharmaceutical industry, innovative and generic drugs can be distinguished. According to the European Medicines Agency (EMA), generic drugs are defined as drugs that are copies of original drugs that have the same active ingredient. Authorization is based on data about efficacy and safety from trials of the innovative drug. APIs are both molecularly and quantitatively the same, and so is their pharmaceutical form, but their therapeutic effects are not entirely the same. Authorized differences are regulated by law and are checked using bioequivalence testing. A company can only market a generic drug if the ten-year data and market exclusivity period of the original drug has expired (EMA, 2020a). Furthermore, it is important to note that EMA requires generic drug manufacturers to provide information on the quality of the drug—i.e., to provide evidence that the generic drug leads to the same level of API in the human body as the reference drug (EMA, 2020b). The US Food and Drug Administration (FDA) uses a very similar definition to the EMA (Food and Drug Administration, 2018).

Generic drugs increasingly became the focus of various interest groups in the second half of the twentieth century with a view to ensuring that patients receive the same treatment at a lower cost (Bongers-Carradinha, 2009). However, studies show that the growth of this market has been slow (Fischer-Stargardt, 2016). In this context, research into consumer behaviour regarding the generic drug purchasing process has attracted the interest of public health policy makers, business leaders, and academic researchers (Aufegger et al., 2021; Kauppinen-Räisänen et al., 2012), especially in countries where regulation encourages the production and marketing of generic drugs.

While generic drugs are gaining ground, pharmaceutical policies that have the aim of cutting costs are becoming increasingly widespread. A significant number of drugs that target major diseases, such as APIs for hypertension and diabetes, have lost patent protection.

The share of generic drugs in the pharmaceutical market varies from country to country. An examination of the situation in 26 OECD countries shows that the share of generic

drugs by value is 25% (average of the sample) and their share by volume is just over half of the total market volume (52%). The UK (85%), Chile (84%), Germany (82%), and New Zealand (81%) are associated with the highest volume share of generic drugs, while Luxembourg (11%), Switzerland (23%), and Italy (21%) have the lowest. In terms of turnover value, the highest shares are found in Chile (64%), Austria (50%), and Latvia (43%); in the other countries, the share varies between 15% and 35%, with only Italy (8%) and Luxembourg (6%) having a turnover value of generic drugs in single digits. Naturally, the difference in the value/volume ratio is due to the difference in the price level of generic products. See Figure 8.

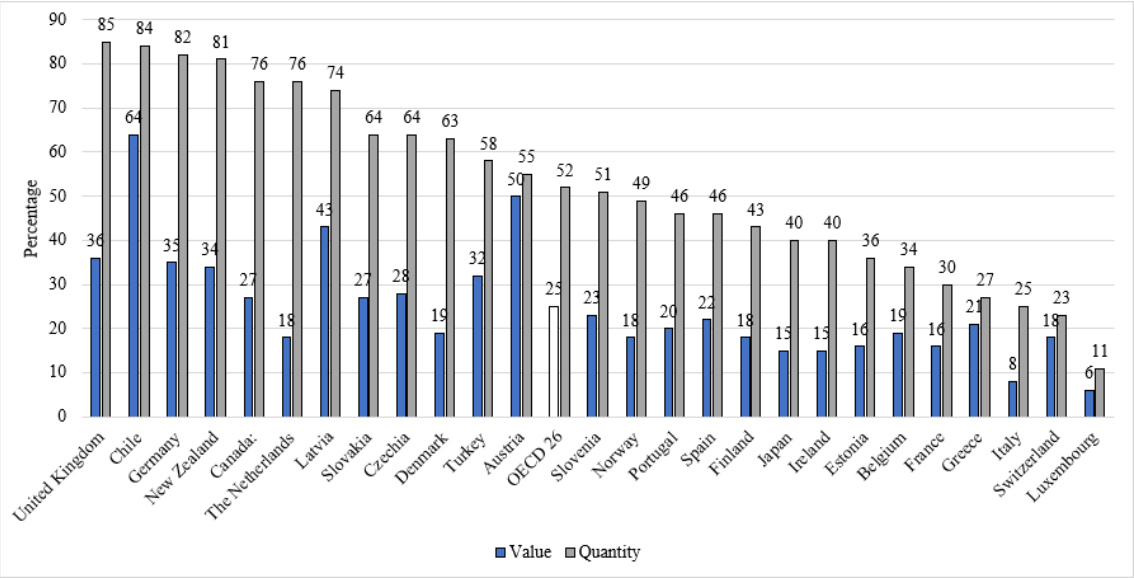


Figure 8 Share of generics within the whole pharmaceutical market, 2017 (or nearest year) (Source: OECD Health Statistics [database], 2020)

The market share of generic drugs varies widely across the world, which is why my aim was to explore nine countries that represent different situations. Thus, I chose Italy (with a low share of generics), France, Spain, Romania, Hungary, the Netherlands, Germany, and the United Kingdom (with the highest share of generics).

Despite the importance of this topic and the growing number of publications on generic drugs, some debate remains (Howard et al., 2018). Obtaining more understanding about the factors that influence attitudes and purchase intentions in this segment has been challenging (Ferreira et al, 2017). Although the important role of attitudes and purchase intentions can provide insight into the maximum use of generic drugs, no article has systematically assessed 'purchase intention', 'attitude', and 'generic drugs' together to provide in-depth knowledge that can be of help when making decisions.

It is also worth mentioning that the range of available therapies has also changed in recent years. An increasing number of specialized, innovative drugs have been developed and brought to market, mainly as therapeutic options for smaller patient populations. The economic impact of such targeted drug therapies must be considered as well as the share of expenditure they account for is increasing, and spending on them now makes up about one-third of all pharmaceutical spending (Belloni et al., 2016; OECD, 2017a).

2.1.4. Seller side – manufacturers

Companies make a profit by satisfying consumer needs. For pharmaceutical companies, consumer need refers to unmet clinical need that can be satisfied by developing, manufacturing, and marketing appropriate drug therapies. The resource requirements of pharmaceutical R&D are substantial, with a significant share of the related expenditure covered by for-profit industry players: for example, in 2009, $240 billion was spent on drug development worldwide, 60% of which was contributed to the private sector (OECD, 2017a). Increasing price competition among generic drugs, the development and market-related difficulties associated with innovative products, and rising costs are driving the need for more efficient operations and competitive product portfolios. As a result, recent years have been characterized by mergers and acquisitions of pharmaceutical companies (Finn, 2016). For companies, it is essential to understand consumer attitudes to and purchase intentions associated with pharmaceutical products (Ferreira et al., 2017; Aufegger et al., 2021; Shekhar et al. 2019)—and the same is true when formulating public health policies and strategies (Greene-Kesselheim, 2011).

For pharmaceutical companies to be successful, Kotler argues, they need to be successful both in terms of their internal corporate structure and their expertise. According to Kotler, ‘the success “hardware” of a company is a dynamic internal corporate structure, a good information, planning and quality system and a good strategy, while the success “software” is the specific expertise, the development of an internal corporate mindset that subordinates everything to working together for common goals and that enables all employees to identify with the common goals and the strategy' (Blaskó, 2011, p. 22). To achieve this, different departments in the company must coordinate their activities to support each other effectively and mutually, and to make their activities—in the process of which marketing plays an important role—easy for users to understand.

2.2. Evidence-based medicine (EBM) and evidence-based drug assessment

2.2.1. Evolution of EBM

According to Botz, the first economic studies that included economic calculations about drugs started to appear in the 1970s. Even these studies recognized that such economic decisions could only be made on the basis of a professionally substantiated, well-developed and critically evaluated set of criteria. Mentioned as a landmark event, a formal provision of drug authorization and evaluation introduced by the Australian authorities on 1 January 1993 required that, in the evaluation of new drugs, economic analysis should be considered (Botz et al., 2008a). This provision can be contrasted with Antalóczy's statement (Antalóczy, 1997) that manufacturers should always meet the key requirements of efficacy, safety, and an adequate side-effect profile.

Following the Australian decree in 1993, similar measures were taken in many countries around the world, including in Hungary, that insurers' pharmaceutical reimbursement should include the element of cost-effectiveness. Further, there is a need, not only economically but also professionally, for optimized and individualized medication, which, based on the available literature and the experience of treating a large number of patients, provides critically evaluated—i.e., evidence-based—medicine during treatment (Botz et al, 2008b). Evidence-based medicine (EBM) as defined officially is 'a methodology for therapeutic practice and clinical decision making based on the collection and critical assessment of the best available scientific evidence (results) to make decisions about the practical application of specific diagnostic, therapeutic technologies (procedures) and other preventive and therapeutic activities' (Glossary of Health Science).

This approach captures the criteria for drugs that satisfy the four requirements of efficacy, safety, quality, and cost-effectiveness, complemented by the optimized choice and use of drugs (Botz et al., 2014).

Due to the growth of scientific knowledge, the range of health services has expanded rapidly, and national economies are not fully able to keep pace. There may be large gaps between those services that are available and those that are reimbursable. The main problem is financing. Pharmaceutical research is costly, which in many cases, especially in relation to innovative drugs, generate high prices; and additionally, drugs must be evidence-based and substantiated scientifically within each and every research project. For this reason, in order to be included on the approved drug list (see the pharmaceutical

policy section), insurers expect pharmaceutical manufacturers to comply with the four requirements: i.e., in addition to the 'basic requirements' of any drug, to meet the requirement of cost-effectiveness too (Botz et al., 2014).

In the EBM approach, which is a major determinant of today's approach to healthcare, physicians combine the best available and systematically processed scientific evidence with their individual clinical experience when making decisions about individual patients and, in consultation with patients, select the optimal treatment (Decsi, 2011; Sackett et al, 1996). More recently, it has been suggested that this decision model should be supplemented by consideration of patients' clinical condition and the circumstances of care, and patients' activities should also be incorporated into the decision-making process, additionally to their expectations (Haynes et al., 2002).

2.2.2. Advantages and disadvantages of EBM

A better understanding of evidence-based medicine reveals several arguments for and against the use of EBM, and as a result, its widespread diffusion may face barriers (Zwolsman et al., 2012).

One advantage of EBM is that it is based on professional recommendations. Thus, it does not imply any commitment to individual products, procedures, or diagnostic methods. Another advantage is the nature of the method, in that evidence is arranged in a hierarchical order. Randomized controlled trials are perceived to be the highest quality form of trials, providing a transparent, high-quality and systematic review. A systematic analysis of currently available evidence is used to determine how effective and safe a product or a procedure is for a certain population. If new findings emerge, they can modify the range of recommended methods, or recommendations can be non-exclusive, or there may be recommendations supported by a similar strength of evidence that are considered therapeutically equivalent (Hajjaj et al., 2010).

According to Botz's research, there are several comprehensive surveys showing that drug prescription, part of the physicians' job, is the task physicians are least satisfied with. One explanation of this is that the vast amount of information that is available makes physicians uncertain about the credibility and the relevance of their knowledge. Incorrect or inappropriate prescriptions can lead to serious professional and economic consequences for doctors. The methodology of evidence-based medicine offers a solution to this problem (Botz et al. 2014, Sackett et al., 1996).

The wide practical application of the principles of EBM is hampered by the fact that the continuous incorporation of the latest advances in medicine into daily clinical practice is obstructed by a number of processes. Among other things, practicing physicians often lack the time to search for relevant information, have limited ability to interpret the results of scientific publications, to resolve inconsistencies in publications, and to translate new findings into practice in line with patients' expectations (Mamdani et al., 2008; Zwolsman et al., 2012).

In the light of the above-mentioned economic implications, it is important to underline that in this approach costs are not considered—in fact, in the often-cited article about the definition of evidence-based medicine by Sackett et al., the authors point out that EBM aims to maximize individuals' quality of life and life expectancy, and consequently may increase health expenditure (Sackett et al., 1996). However, it should be emphasized that although EBM is not intended to optimize costs, it can contribute to better resource utilization. An example of this may be found in a study by Fisher and Avorn, who from a retrospective evaluation of US patient records concluded that more than a billion dollars could be saved on antihypertensives alone if prescribing were better aligned with treatment guidelines (Fisher-Avorn, 2004).

A further disadvantage is that evidence can only be related to a specific product or population; i.e., cannot be transposed to similar products or population. This issue can become manifest when the individual views of patients are considered, since, unlike under the previous system, it is no longer physicians' individual decision only that must be considered. Professionals have to make optimal decisions that take into account not only their own experience but a wide range of other influencing factors. Consequently, EBM increases the difficulty, because with EBM only well-defined professional decisions can be made, into which individualized medicine is not incorporated (Hajjaj et al. 2010). In addition, the aim of this method is to increase the quality of care and to achieve the highest possible effectiveness of care, but this is not always a cost-effective technique (Decsi, 2011; Medical Online, 2010; Fekete, 2013). Botz's work refers to another disadvantage of the procedure; namely, that the concept of evidence is not clearly defined, and there is no baseline data for all problems. There may be cases when EBM is misinterpreted, resulting in a mechanistic approach to therapies that may overshadow physicians' experience and undermine patient-centred care and the physician-patient relationship.

Negative criticisms of the approach mainly stem from a lack of knowledge and inappropriate interpretations. However, the literature shows that evidence-based medicine

has become an increasingly dominant and well-known method in healthcare. When providing treatment for a defined group of patients, EBM-based analyses are beneficial, as they ensure that vital factors are not overlooked (Botz et al., 2014; Mamdani et al., 2008).

In current practice, it is mostly up to the individual physician to decide whether to use this method. Obviously, the impact of EBM is reflected not only in the scope of individual discretion but also, for example, in professional guidelines and institutional protocols for the use of drugs. It is worth exploring further the extent of the influence of the method on drug-prescribing habits.

In conclusion, evidence-based medicine has more advantages than disadvantages, and its application is therefore of benefit to medicine as an activity, including in supporting the interests of patients.

2.2.3. Clinical ranking based on EBM principles

Studies from 2016 and 2017 suggest that, based on clinical meta-analyses, APIs can be ranked according to efficacy and safety (Kovács-Simon, 2017). My hypothesis is that, in the long term and under appropriate competitive conditions, the positive attributes of clinically more effective and safer APIs should be reflected in the sales of drugs. To create a rank order of clinical appropriateness, the principles of evidence-based medicine were followed.

Based on the above assumption, this aspect should be of key consideration in the use of drugs. Although drugs that act on the same point of intervention theoretically show strong similarity, due to their different chemical structure they can behave differently in the human body, either pharmaco-kinetically or pharmacodynamically—consequently, the importance of evidence-based medicine is further strengthened. It is difficult to address this issue adequately, as defining clinical sequences is not always a simple task. It is not certain, for example, whether the same quality of clinical evidence is available for each API. Similarly, this is the case for ACE inhibitors.

Although these drugs are all registered for hypertension treatment, not all of them are supported by clinical data in relation to their use for treating other diseases, such as improving survival after heart failure or myocardial infarction (Furberg-Pitt, 2001; Furberg-Psaty, 2003; Dinicolantonio et al, 2013). However, professional guidelines usually give recommendations about hypertension medication at the class level of APIs,

even when individual APIs are listed in the evidence review (Stephan et al., 2015; Mancia et al., 2013; Mancia et al., 2007; Chronic kidney disease in adults: assessment and management, 2014; Hypertension in adults: diagnosis and management, 2011; Kiss, 2015).

From a practical point of view, there may be arguments in favour of class-level recommendations, as the messages transmitted by the related directive can be simplified, they can be made more transparent, and physicians are required to remember less data. However, the disadvantage of class-level recommendations is that no distinction is made on the basis of differences between individual APIs, and the optimal recommendations may not be made from a clinical point of view. Maggioni et al. revealed, based on prescribing data from OECD countries, that nearly a quarter of patients with heart failure received an inappropriate dose or no doses of ACEI or ARB treatment compared to what was recommended in the treatment guidelines (Maggioni et al., 2015). Nevertheless, this does not mean that physicians do not consider the available evidence or follow guidelines without justification.

Bradley conducted interviews with GPs in the UK about prescribing decisions that cause discomfort; nearly a quarter of responding physicians said that they were not entirely comfortable with prescribing cardiovascular drugs (only benzodiazepines and antibiotics were mentioned more frequently). Among the concerns about prescribing, half of the physician mentioned side effects, 40% referred to cost, and a quarter of them had doubts about the appropriateness or the necessity of the drugs, with 15% having doubts about efficacy (Bradley, 1992). Ab et al., who interviewed GPs in the Netherlands, found that there were a wide variety of reasons for not prescribing lipid-lowering drugs to diabetics despite the clear recommendations in the related guidelines. In addition to missing, incorrect, or uncertain knowledge, the authors identified several reasons for physicians' decisions that could be considered rational arguments, such as the existence of contraindications or the risk of drug interactions and side effects (Ab et al., 2009).

To compare drug therapies in my doctoral research, it was first necessary to establish their scientific ranking in terms of efficiency and safety. For this purpose, clinical meta-analyses, other scientific comparative studies, and professional guidelines associated with the relevant indication were identified in line with literature recommendations. Obviously, the results of randomized clinical trials and their higher-level systematic analyses, such as meta-analyses, are the key to comparing therapies. Clinical literature was categorized according to the internationally accepted classification system for

evidence-based medicine (Botz et al., 2014), and the order of clinical appropriateness was calculated on the basis of weights used in the classification system (Kovács, 2017).

Level of evidence	Definition
1++ (1A)	Results are from high-quality meta-analyses, systematic literature reviews, or multiple randomised trials with very low potential for systematic errors (bias).
1+ (1B)	The results are from a well-designed meta-analysis, systematic literature review, or multiple randomised trials with a low potential for systematic errors (bias).
1- (1C)	The results are from a well executed meta-analysis, systematic literature review, or multiple randomized trials with a high potential for systematic errors (bias).
2++ (2A)	Results are from a systematic literature review of good-quality cohort or case-control studies, or from good-quality cohort or case-control studies with a very low probability of systematic errors and confounding effects and a high probability of a causal relationship between evidence and conclusions.
2+ (2B)	The results are from well-executed cohort or case-control studies with a low probability of systematic errors and confounding effects and a medium probability of a causal relationship between evidence and conclusions.
2- (2C)	The results are from cohort or case-control studies with a high probability of systematic errors and confounding effects and a high probability of a non-causal relationship between evidence and conclusions.
3	Results are from non-experimental studies, e.g. case studies, case series.
4	Results are based on professional opinions (expert opinion of expert panels, research groups, or leading individual(s) of the special field.

Figure 9 Internationally agreed system of recommendation associated with category classifications (Arabic numeral = suitability of type of study, letters and '+' and '-' signs = quality of evidence; Source: Botz et al., 2014)

These classifications were applied as a basis for determining a scientific ranking. The clinical appropriateness of therapies is considered universal in this research. (For example, potential differences may be based on the fact that members of different ethnic groups may respond differently to certain drug therapies. In my doctoral research, this effect is not considered.) From a medical point of view, the use of ARBs is recommended over ACE inhibitors due to their more favourable side-effect profile. Additionally, the clinical ranking of drug therapies with ACE inhibitors is also shown in detail in Figure10).

ARB > ACE inhibitors

ACE inhibitors	Rami-pril	Enalapril	fosino-pril	Lisinop-ril	Perindo-pril	Zofeni-pril	Capto-pril	Trando-lapril	Benaze-pril	Quina-pril	Moexi-pril
Clinical Rank	1	2	2	2	2	2	3	4	5	5	5

Figure 10 Summary of relationships between clinical evidence

2.3. Life cycle of drugs, and competition between innovative and generic therapies

New drugs are launched at the end of a long process of research and development. Market entry is conditional on obtaining marketing authorization, and the framework for competition is mainly determined by the protection of industrial property rights (IPR).

2.3.1. Framework for the protection of industrial property rights, and drivers of pharmaceutical innovation

Of all industries, the pharmaceutical industry spends among the most on innovation (DiMasi et al., 2016). Following the Trade Related Aspects of Intellectual Property Rights agreement (TRIPS) (1994) (Smith et al., 2009), many countries regulated patent protection for pharmaceutical products, which has played an important role in encouraging investment into clinical studies and research (Brekke et al, 2009.) The manufacturing process of most pharmaceutical products can easily be replicated with less investment than that required for the original patented product (Lionberger, 2008). Once the patent-guaranteed exclusivity period expires, generic pharmaceutical companies start to intensify competition in the market (Kanavos, 2014), leading to price reductions (Scherer, 2000; Dunne et al., 2013)—although there are examples when this is not the case (Rizz-Zeckhauser, 2009)—and improving access to essential pharmaceutical products (Desai et al., 2018). Without an IPR framework, manufacturers would not be interested in bringing novel products to market, as the cost of development would not be recovered.

‘Intellectual property is a legal relationship with an absolute structure, similar to property rights, whose system of rules, established within the field of civil law, provides legal protection to the creators of intellectual works by granting exclusive property and inherent rights’ (Website of the Hungarian Intellectual Property Office). In many cases throughout history, knowledge about a market advantage was protected by secrecy (e.g. through a guild). However, one should now recognize, especially in the present information-driven world, that secrecy cannot sufficiently protect the products of creative minds.

‘Patents provide legal protection for inventions’ (Pintz, 2005). It is important to note that a patent does not give the manufacturer the right to make or use something, but gives the patent-holder the right to prohibit others from making, using, marketing, or storing an invention for that purpose (Szarka, 1994). By excluding competitors, a monopolistic market can be legally created. In most countries, the protection period is currently 20

years from the date of patent filing, with the possibility of an extension of up to five years in many countries under certain conditions.

2.3.2. Marketing of drugs, data exclusivity

Marketing authorization ensures that marketed pharmaceuticals are safe, effective, and quality-assured. During the authorization process, the aim of the drug authority is to evaluate the results of chemical-pharmaceutical and pre-clinical research, as well as clinical trials regarding the formulation. The marketing of pharmaceuticals is subject to the fact that the authority considers both the manufacturing process and the formulation, as well as the risk-benefit ratio of the pharmaceuticals to be appropriate based on the available experimental data (DiMasi et al., 2016). Marketing authorizations are required for innovative and generic manufacturers alike. The complexity of the information to be presented for the authorization of the two categories differs because, in the case of innovative molecules, a full R&D dossier has to be presented. In contrast, for a generic application a large body of knowledge can be referred to in relation to the original development process.

Besides patents, data exclusivity is also designed to ensure protection for innovative drugs. While patents protect innovation in relation to drugs, data exclusivity protects business secrets regardless of the innovation. Data exclusivity applies to data provided by the innovative manufacturer. These data cannot be accessed and used by generic pharmaceutical manufacturers. In practical terms, data exclusivity therefore prevents, for a certain period, authorities from registering generic manufacturers' products. The period of exclusivity in the European Union, according to the amendment to the community code related to medicinal products (Directive 2001/83/EC) which entered into force in November 2005 (Directive 2004/27/EC), is eight years from the first authorization of a 'European reference medicinal product', plus an additional two years of market exclusivity (together, ten years of effective market exclusivity), which may be extended for up to one more year in certain cases.

2.3.3. Research and development in the pharmaceutical industry, and the evolution of competition

Regarding the market launch of a new drug, people usually think of one product—i.e., a single development by a single manufacturer. However, this does not necessarily mean that the drug is entirely new in term of chemical structure, mechanism of action, or therapeutic potential. Additional to first-in-class drugs (Petrova, 2014), other original

drugs with a different API but similar mechanisms of action can also be introduced to market. Some of them are the outcomes of the parallel development of rival pharmaceutical companies (‘me-too products’) (DiMasi-Faden, 2011), as R&D projects can be initiated almost simultaneously in several locations based on common psychological or medicinal chemistry knowledge and may result in similar solutions. In other cases, however, molecules belonging to the same class of API are not the outcome of parallel development but rather of a conscious strategy. These are so-called ‘follow-on’ molecules, which are usually better or different in some properties than previous ones (Petrova, 2014). In principle, me-too and follow-on drugs are expected to increase the therapeutic options on the market, thus they contribute to well-being and induce price reductions, and their regulatory acceptance encourages development. However, some believe that they fail to represent genuine innovation, and that the related price competition may not be effective, as in certain cases they may lead to higher expenditure (Arcidiacono et al., 2013; Bergua et al., 2012; Morgan et al. 2005).

Thus, for a given therapeutic target, competition may first emerge at the level of the active substance. The degree of competition depends mainly on the business potential of the therapeutic area, which in turn is determined by unmet medical needs.

2.3.3.1. Research and Development

On average, an initial drug development process can take about 13.5 years, during which time the drug candidate is not profitable. The R&D process defined by unmet needs can be broken down into the following stages (Borsi et al., 2004):

Discovery: From a large number of synthetically produced candidate molecules, a lead molecule needs to be selected for subsequent clinical trials from which a formulation can be developed.

Pre-clinical phase: Carrying out pharmacological (pharmacokinetics, toxicity, metabolite) trials of the selected compound under laboratory conditions.

Trial phase I: The first phase of the human clinical trial. The pharmacokinetic and safety (dosage) properties of the new API are investigated on a small number of healthy human subjects.

Trial phase II: Investigating the efficacy and safety of the molecule on a small sample of patients.

Trial phase III: Efficacy and side-effect trials on large samples of up to tens of thousands of individuals.

Registration: Regulatory procedures whereby an authority can issue a marketing authorization that imposes conditions on the marketing of the drug. Once a marketing authorization has been granted, the drug can be put on the market for the indication concerned.

Trial phase IV: Once a drug has been put on the market, safety studies are required for a further 2–3 years to detect adverse reactions. This is also called post-marketing research.

It is very important to note that development costs are huge. DiMasi et al. (in perhaps the most cited paper on the subject) estimated development costs in 2003 at more than $800 million (DiMasi et al., 2003). Since then, the cost has grown even further, and in 2006, for example, biotechnology research was estimated to cost over $1.3 billion, with subsequent research estimated to cost over $2 billion. The result of this estimation is highly dependent on the methodology, with DiMasi et al. estimating the average annual increase in the cost of biotechnology research of 8.5% in excess of inflation (DiMasi et al., 2016). The success rate of drug development increases in line with successive clinical phases. Approximately 1 in 4,000 APIs that reach the pre-clinical stage enter the market. Of those that enter phase I trials, 26% are registrable, while 57% of those that enter phase III trials are registrable (Abrantes-Metz et al., 2005). It can therefore be said that companies can be more successful if they withdraw their unsuccessful compounds from development and complete the development of successful compounds as soon as possible (McCarthy, 2004),

Marketing plays a very important role even at this stage, but it should be noted that the marketing tasks that follow product development may differ from one drug to another. (Becker-Lillemark, 2006) If we consider, for example, the mapping of consumer needs, in the classic case this can be done by looking at the characteristics of individuals and groups, whereas in the case of medicines need is scientifically defined by the doctors. (Vágási et al., 2006) (‘Medicine is not an object of desire, [unlike with] most consumer goods, but a real need’ [Borjádi-Juhász, 2003]). Therefore, in many cases the acquired marketing knowledge should be applied in a completely different way to drugs than to other products. Strategic price decisions, which are presented in the section on pricing, are also introduced at this stage.

2.3.3.2. Market introduction, growth, maturity

The importance of operational pricing and patent renewal is increasing, particularly in the case of successful drugs. The biggest challenge, however, is to break the product awareness barrier and then to steadily increase the number of consumers. This task, even for an effective and safe drug, can fail if the right marketing is not in place. This is the stage at which it transpires whether the marketing strategy of the company is on the right track, and also when operational marketing is constantly being evaluated. As for prescription drugs, it is very important to attract the right opinion leaders and to build the right sales representative base, while for OTC drugs advertising is also very important.

2.3.3.3. Decline

Decline occurs when demand for a product starts to fall (Bauer et al., 2016). This is also a different phenomenon in the life cycle of drugs compared to general products. The decline of innovative products starts with patent expiry and the market entry of generic manufacturers. However, for the purposes of my research, it is very important to note that for generic manufacturers this entry point marks the beginning of their market presence and the start of growth in market performance.

Thus while for an original brand decline is a relevant process, this is not necessarily the case for API, as generic competitors will also market the same API with their own products (generic brands). Therefore, from a marketing point of view, the level of competition starts to change. As long as the patent is protected, the API is typically marketed under a brand name. Competition within the therapeutic class takes place at the level of the patented API, and the innovative brand and the API brand can be considered to be equivalent (intra-need group competition). As patents expire and generic products enter the market, competition at the level of the existing APIs moves to the level of brands. When several APIs within a therapeutic class are on the market, the dynamics of competition may vary significantly over time and across countries due to different patent expiry dates. Competition within a product class therefore contributes further to priorly existing forms of competition.

Figure 11, based on Grabowski and Gronde (Grabowski et al., 2002; Gronde et al., 2017) illustrates the three main stages of the life cycle of an innovative product (see Figure 11).

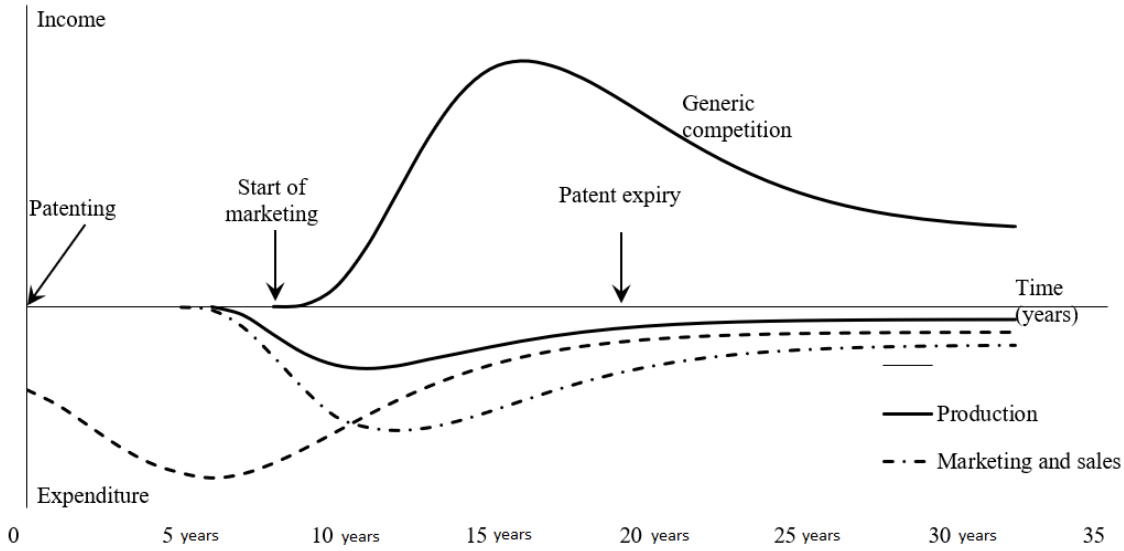


Figure 11 Life cycle of innovative drugs (based on Grabowski 2002 and Gronde 2017) (Grabowski et al., 2002; Gronde et al., 2017)

2.3.4. Generic competition in the pharmaceutical industry

As long as the patent term of the drug or the data exclusivity or market exclusivity lasts, generic competitors will not be marketed. As innovation costs are enormous, the period until generics can enter the market is of great importance for originators, since this is the period when they can recoup their investment.

The development cost of generic drugs is typically much lower than that of original ones, and generics are introduced to the market at a lower price as well (Kanavos et al., 2008). The number of generics entering the market varies with the size of the market: originator products with higher sales figures encourage more generic competitors to enter the market (Grabowski-Kyle, 2007). Reiffen and Ward, from a study of data about 31 drugs that became generic in the US between 1985 and 1992, found that prices decrease with an increase in the number of competitors on the market. According to their model, in a generic market with ten or more players, the price is close to the marginal cost of production, but the price can be as much as 20–30% higher if only one generic is present (Reiffen-Ward, 2005).

Consequently, the end of the monopolistic position of an originator product leads to lower pharmaceutical spending on generic drugs. In turn, lower prices may lead to easier access to drugs and increased sales of the API (European Commission, 2009; Conti-Berndt, 2014).

However, it cannot be concluded that as generic competition begins only price reductions occur or that the ideal principles of free competition come into existence. With the entry of generic drugs, the price of the original branded product usually remains unchanged, or even starts to grow (the 'paradox of generics'). This may be due to the profitability of the continued sales of the originators, as prescribers responsive to the marketing communications of the pharmaceutical company continue to prescribe the original brand (Kanavos et al., 2008). Gonzalez et al. attributed the decline in overall sales of the API at the end of the patent protection of Prozac to the lessening of marketing activity associated with the original brand. Their analysis revealed that the marketing communication of competing pharmaceutical companies for their antidepressants with other APIs encouraged responsive prescribers to order other brands still under patent protection (Gonzalez et al., 2008). Also, for the US market Duflos and Lichtenberg described how the combined sales of original brands and generics remained unchanged after the launch of the latter. In their view, generic drugs tend to push down prices, which could facilitate consumption, but at the same time the originator starts to slow down marketing activity (Duflos-Lichtenberg, 2012).

Following the expiry of a patent, some time is needed until prices start to go down. The speed of this depends on the price of the product before the patent expires, and the market size, which factors define how attractive it is for generic firms to enter the market with cheaper versions of the product (Hudson, 2000). Generic producers may not find a very small market size sufficiently attractive to enter the originator's market, thus the innovator can remain the sole distributor of the drug for a longer period (Grabowski-Kyle, 2007). For the first generics, average duration until market entry may vary from country to country, as may the extent of the prescription of generic drugs (generic penetration) (Kanavos, 2014). Furthermore, even generic firms can reduce competition by acquiring competitors, which in extreme cases can lead to the monopolistic position of the acquirer and a huge price increase: this is what happened with albendazole and digoxin in the US (Alpern et al., 2014).

To protect their markets, innovative manufacturers attempt to defer the market entry of generic drugs using different methods. In addition to obtaining additional market protection (i.e., by registering a new or paediatric indication), a number of methods that are used to influence competition have been reported over the past decades. For example, the introduction of a new, patent-protected pharmaceutical form through family extension and then switching patients to protect part of the originator's own market before

genericization (‘product hopping/evergreening’). In the US, it is typical for companies to launch generic versions of drugs themselves or to contract with a generic manufacturer, allowing the latter to use their patents to enter the market before other competitors (‘authorized generic’), thus taking advantage of the 180 days of market exclusivity for the first generic submission (Jones et al., 2016; Hess-Litalien, 2005). Additionally, several methods have emerged that may raise different competition law concerns. Examples of patent manipulation include when the originator uses patents that do not contain significant innovation to make market entry more difficult, or makes out-of-court settlements (patent settlements) with manufacturers who are about to enter the market to prevent them from challenging their patents and bringing their products to market (Jones et al., 2016; Hess- Litalien, 2005). In the European market for ACE inhibitors, such practices—using patents to hinder generic competition—have recently been revealed. Servier, the developer of perindopril, has filed a number of patent applications for the production of their API which involved no real innovation and were aimed at preventing generics from entering the market, while at the same time tried to acquire technologies that could circumvent patents. Between 2005 and 2007, Servier also concluded patent agreements with pharmaceutical companies who were considering entry to the generic market. Finally, in 2014 the European Commission fined Servier and the company that entered a patent agreement more than €400 million for violating competition law (Summary of Commission Decision of 9 July 2014, 2016).

As cheaper bio-equivalent formulations offer the opportunity to reduce expenditure and improve access to therapies, health policy awards high priority to the use of generic drugs. Therefore, measures for promoting the use of generic drugs can often be identified in connection with the regulations of pharmaceutical markets. According to Kobayashi et al., people usually have difficulty accepting generic drugs, with patients often believing that reference products are of better quality and safer than the former (Kobayashi et al., 2011).

2.3.5. Diffusion of drug therapies, ARB and ACE therapies

According to Rogers’ diffusion model (see Figure 12), which is popular in research into the diffusion of innovation, innovations spread throughout societies through various communication channels over time (Haider-Kreps, 2004). By plotting the proportion of new technology users over time, the model describes (by default) a sigmoid curve as the five groups distinguished by their attitudes towards the new process (in our case, the new drug)—innovators, early adopters, early majority, late majority, and laggards—begin to

adopt the innovation (Rogers, 1983). At the individual level, five stages of the adoption process are distinguished, from awareness of the new option to commitment to use: acquisition of knowledge, persuasion, decision to reject or adopt, implementation, and confirmation. Following this train of thought, Rogers' model combines macro-level processes with micro-level events, which, when applied to the pharmaceutical market, can lead to the market penetration of innovative drugs from individual medical therapeutic decisions.

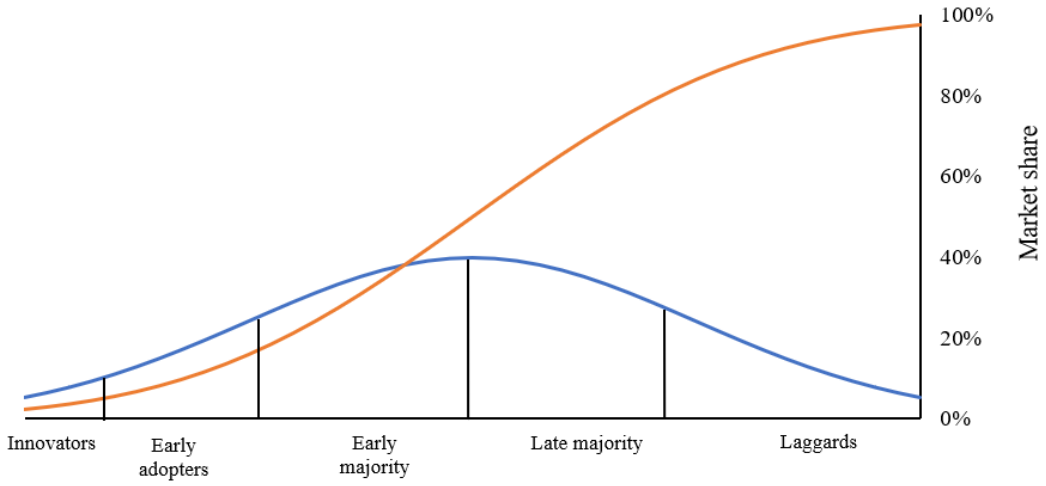


Figure 12 Schematic representation of the diffusion of innovation according to Roger's model

Thus, the pharmaceutical market is driven by constant innovation and cannot be reduced to the interaction between the supply of original drug manufacturers and the demand of patients hoping for a cure. On the manufacturing side, competition between generic players is becoming increasingly fierce, alongside the emergence of innovative companies.

To assess the evolution of the market performance of the two classes of antihypertensive therapies, it is necessary to provide a brief summary of their history. Of the two mechanisms of action, ACE inhibitors were the first therapies to be approved and introduced in the early 1980s (captopril, enalapril in 1980–1981, lisinopril, perindopril and ramipril in 1987–1988–1989; these were followed by other molecules). ACE inhibitors lost their patent exclusivity mainly in the 1990s and early 2000s. In some cases, manufacturers even tried to extend patent protection through violating the law. ARB entered the market first in 1995 with losartan (with valsartan in 1996, and with candesartan in 1997). Losartan and candesartan became generics in the early 2010s. By

2016, all major ARBs had become generic. Innovative and generic market entries determine market patterns in a very complex way.

2.4. The impact of pharmaceutical policy instruments on different pharmaceutical markets

Various regulations and policies are needed to ensure affordable access to safe drugs. Public involvement in the research and development of drugs is of key importance: it provides the basis and sets the schedule for access to new medicines (WHO, 2018).

2.4.1. Financing

The role public authorities play in the pharmaceutical market is different from country to country around the world. Looking at pharmaceutical policy in the developed world, two basic models can be distinguished. In the model specific to EU Member States, governments are the primary financiers of medicines (Chintagunta-Desiraju, 2005), whereas in the US, the private insurance system is the predominant driver. In other words, while in Germany, France, and Hungary, for example, drugs are typically paid for out of the public (i.e. state) pocket, in the US people pay a predetermined monthly premium for various private insurance plans and a consumer contribution when buying drugs (Wosinska-Huckman, 2004).

In Europe, there are two main types of healthcare systems: one based on social health insurance (SHI)—for example, in France, Germany, and in many Eastern European countries—and one based on a national health service (NHS), as found in Italy, Spain, and the United Kingdom. The main difference lies in the eligibility to services: under the NHS systems there is no link between tax payment and eligibility for services, while under SHI systems there is (WHO, 2018).

Compared to other regions, many countries in the WHO European Region have high levels of healthcare coverage (OECD, 2016). Some countries in Western Europe (namely, Austria, Belgium, France, and Germany) have SHI systems ('Bismarck systems') to provide social care. In the 1990s, SHI was introduced into several countries in Central and Eastern Europe and in the CIS-countries. SHI is a healthcare financing system, often financed by insurance contributions from employers, employees, and public subsidies. In many countries with a SHI approach, mandatory schemes apply to (employed) persons whose income does not exceed a certain threshold (compulsory insurance). SHI is delivered through various health insurance providers (i.e., health insurance institutions

and sickness funds). In some countries, patients have to choose a health insurer (as in Germany), while in others patients are assigned to a specific health insurer, for example on the basis of their occupation (namely, Poland) (WHO, 2018).

NHS schemes are financed by general (central or regional) taxation, usually for all residents. The range of services that is provided is the same for all individuals concerned, and services are often provided by public institutions. Apart from the United Kingdom, some Mediterranean countries (including Italy, Spain, and Portugal) and some Nordic countries (including Denmark, and Sweden) have NHS-based health systems. Voluntary health insurance can play a role in any health system (WHO, 2018). See Table 2.

Table 2 Healthcare in nine European countries, 2017 (Source: WHO, 2018)

Country	NHS / SHI	Single-payer (S) or multi-payer (M)	Competitive SHI	Proportion of population covered by public health insurance
United Kingdom	NHS	S	N/D	100%
France	SHI	M	No	99.90%
The Netherlands	SHI	M	Yes	99.80%
Poland	SHI	S	No	91.30%
Hungary	SHI	S	N/D	95%
Germany	SHI	M	Yes	88.9% (public) 10.9% (private)
Italy	NHS	S	N/D	100%
Romania	SHI	S	No	86%
Spain	NHS	S	N/D	99.1% (public) 0.8% (private)

An important point to discuss about the role of government policy is that prescriptions can also be greatly influenced by medical guidelines that are developed through collaboration between public authorities and professional associations. The main purpose of these professional guidelines is to influence the decisions of prescribing doctors. (Spurling et al., 2010) However, it is always particularly important to consider the underlying interests of various guidelines (e.g. professional interests may be complemented by the need to reduce pharmaceutical expenditure, lobbying by pharmaceutical manufacturers, etc.).

2.4.2. Eligibility

The main means of ensuring that patients have affordable access to drugs is the reimbursement eligibility list, which specifies the drugs selected for reimbursement

(positive list) or lists the drugs explicitly excluded from reimbursement (negative list). All the studied countries in the WHO European Region have at least one reimbursement list, usually in the form of a positive list (WHO, 2018).

- Countries that use a positive list: Armenia, Albania, Austria, Azerbaijan, Belarus, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece (positive list, list of over-the-counter medicines), Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Moldova, Romania, Russia, Serbia, Slovenia, Slovakia, Sweden, Switzerland, Tajikistan, Turkey, Ukraine, Uzbekistan
- Countries that use a negative list: Germany (negative list of prescription-only drugs; non-prescription drugs can be reimbursed in exceptional cases)
- Countries that use both positive and negative lists: Spain, United Kingdom

Four types of reimbursement eligibility are usually distinguished:

- Product-specific eligibility: Drugs are considered either to be reimbursable (costs paid in part or in full by a third party) or not reimbursable. The reimbursement status of each drug is determined by the authority competent for drug reimbursement or by a third-party payer. Most European countries rely primarily on such a system (France, Spain, Italy, etc.).
- Disease-specific eligibility: In this approach, the reimbursement status of the drug and the reimbursement rate are linked to the disease being treated. The same drug can be reimbursed at different prices depending on the patient's disease. In the Baltic States and Malta, this system is mainly used in outpatient care. Some other countries, such as France, it is used as a secondary condition.
- Population-group-specific eligibility: Under this scheme, certain population groups are entitled to a reimbursement rate of 100%, or a higher rate than the standard reimbursement rate. Eligible population groups may be based on conditions (i.e., chronic, or communicable diseases, disability, pregnancy), age (i.e., children, elderly), status (i.e., retired, war veterans) or financial circumstances (i.e., low-income, unemployed). Population-group-specific reimbursement is a very important system, for example, in Cyprus and Ireland. Several European countries, including Latvia, have adopted some elements of a

population-group-specific eligibility approach to complement other key programmes.

- Consumption-based eligibility: Under this approach, reimbursement coverage increases with the increase in drug consumption, determined by the gross drug-related costs of the insured patient over a defined period (usually one year). Once the patient has reached a defined out-of-pocket payment threshold (the so-called 'safety net'), the third-party payer covers all or part of the patient's additional drug costs for the remaining period. Consumption-based eligibility schemes protect patients with greater need for pharmaceutical care (such as chronically ill patients) from excessive out-of-pocket payments. In Denmark and Sweden, consumption-based reimbursement is the predominant approach in the outpatient sector.

Product-specific eligibility was the primary condition in 31 of the 45 countries surveyed by the WHO, making it the most popular criterion for eligibility of the four. In addition, there are four countries (Denmark, Ireland, Sweden, and Kazakhstan) where this type of condition is a secondary condition. Its popularity is due to its transparency, which helps to avoid abuse.

In half of the remaining fourteen countries—in seven cases—disease specificity is the primary criterion. The approach is mainly found in the Baltic States and the post-Soviet Asian republics. Population-group-belonging is a primary condition in only three countries: Cyprus, Ireland, and Turkey. Consumption-based reimbursement is supported primarily by the Nordic countries: Denmark and Sweden (WHO, 2018).

Table 3 Forms of drug reimbursement in nine countries (Source: WHO, 2018)

Country	Product-specific	Disease-specific	Population group based	Consumption-based
United Kingdom	*	-	+	-
France	*	+	-	-
The Netherlands	*	-	-	-
Poland	*	+	+	-
Hungary	*	+	+	-
Germany	*	+	+	
Italy	*	-	-	-
Romania	*	+	+	-
Spain	*	-	-	-

* Primary condition, + Secondary condition, - Lacking condition

The competent authorities responsible for reimbursement and/or the public purse decide whether to subsidize a drug after receiving an application from the marketing authorization holder. Decision-making is often supported by expert committees (reimbursement committees), which may include representatives of other authorities and interested parties. The decision usually concerns both the reimbursement status and the level (reimbursement price) of reimbursement—i.e., whether a drug is considered eligible for reimbursement and the extent to which it is financed by the state. In European countries, the main criteria used to determine the status and level of reimbursement include the therapeutic value of the drug (including in comparison with existing alternatives), medical necessity/priority, safety, cost-effectiveness, and budgetary impact. A growing number of countries are using health technology assessment (HTA) to underpin reimbursement decisions (WHO, 2018).

2.4.3. Drug reimbursement

Most drugs would be unaffordable to consumers if they had to pay the producer-determined price, as well as the wholesale and retail margins and VAT. This is the reason why the more developed countries established various reimbursement schemes decades ago.

Just because a patient is entitled to reimbursement for a drug does not mean that this automatically implies a 100% reimbursement rate. In general, patients have to pay a certain share of the price of a drug. There are several types of co-payment (patient contribution) systems in the outpatient sector:

- Fixed co-payment (Austria, Croatia, Cyprus, Germany, Italy, Italy, United Kingdom)
- Percentage-based co-payment (Albania, Armenia, Belarus, Belgium, Bulgaria, Czech Republic, Israel, Kyrgyzstan, Lithuania, Luxembourg, Portugal, Moldova, Romania, Russia, Slovakia, Slovenia, Spain, Ukraine)
- Deductible (the Netherlands)
- Fixed and percentage-based co-payment (Estonia, France, Greece, Hungary, Latvia, Poland, Serbia, Turkey)
- Fixed co-payment and deductible (Ireland)
- Percentage-based co-payment and deductible (Iceland, Norway, Sweden, Switzerland)
- Fixed, percentage-based co-payment and deductible (Denmark, Finland)

- No co-payment (Malta, CIS-countries)

The inclusion of a drug on the positive outpatient list does not automatically guarantee that the full cost will be covered by the public financier. Drugs on the positive list are only partially reimbursed (up to a fixed percentage). In fact, only a few European countries—Austria, Croatia, Cyprus (public sector only), Germany, Ireland, Italy, Malta (public sector only), the Netherlands, and the UK, as well as a few CIS-countries with a more limited public sector—cover 100% of the cost of all publicly reimbursed drugs. However, other co-payments resulting from a reference price system, such as prescription charges, deductibles, and/or fees, may also apply. It should also be noted that the range of drugs eligible for reimbursement and those covered by the public sector can vary considerably (WHO, 2018).

Table 4 Reimbursement rates of outpatient drugs in nine countries (Source: WHO, 2018)

Country	Reimbursement rate
United Kingdom	Percentage reimbursement rates are not applied
France	100%, 65%, 30%, 15%[a]
The Netherlands	Percentage reimbursement rates are not applied
Poland	100%, 70%, 50%[a]
Hungary	100%, 90%, 80%, 70%, 55%, 50%, 25%[a]
Germany	Percentage reimbursement rates are not applied
Italy	Percentage reimbursement rates are not applied
Romania	100%, 90%, 50%, 20%[a]
Spain	100%, 90%, 40–60% (income-related rate)[a,b]

[a] Additional deductibles are possible due to a reference price system.
[b] Spain provides 100% reimbursement for the unemployed without benefits, people who receive the lowest social pension, and people with occupational diseases.

Most of the studied countries use a limited number of decision-related criteria to determine their drug-reimbursement practices. The commonly assessed criteria are as follows (WHO, 2018):

- Therapeutic benefits of the drug and/or relative therapeutic benefits (added value compared to existing alternatives)—the Netherlands, Poland, Spain
- Medical necessity/priority—the Netherlands, Poland
- Safety—the Netherlands, Poland
- Cost-effectiveness—the Netherlands, Poland, United Kingdom
- Budgetary impact—Poland

In certain countries, drug procurement is decentralized in in-patient care, thus decisions are made by hospitals or hospital owner organizations (namely, Austria, Iceland, Czech Republic). There are other systems where drugs are purchased centrally and decisions are made by the health insurance fund (i.e., Serbia) or even at regional level (i.e., Sweden). It is also common practice for hospitals to maintain direct contact with pharmaceutical manufacturers and negotiate individual prices (WHO, 2018). The following table (Table 5) gives a summary of the proportion (percentage) of reimbursement for the therapies included in the doctoral research and in the countries under study.

Table 5 Reimbursement rates for hypertension therapies in nine countries (Source: Pharma 14 database)

Country	ACE mono	ACE combi	ARB mono	ARB combi
France	65%	65%	65%	65%
Germany	100%	100%	100%	100%
Hungary	80%	80%	55%	55-90%
The Netherlands	100%	100%	100%	100%
Italy	100%	100%	100%	100%
Poland*	20-100%	20-95%	20-100%	30-90%
Romania	50%; 90%	50%; 90%	50%; 90%	50%; 90%
Spain**	40-50-60-90%	40-50-60-90%	40-50-60-90%	40-50-60-90%
United Kingdom	100%	100%	100%	100%

* Fixed rate of reimbursement, the proportion depends on the price of the drug
** Based on the patient's annual income

In every country, the list of reimbursed drugs for in-patient care is a positive list, albeit with differences in in the list for outpatient care, although the specific example of Finland shows that there are countries where all drugs used in hospitals are funded by the hospital (WHO, 2018).

Agreements between pharmaceutical manufacturers and the healthcare provider (Managed Entry Agreement) ensure that uncertainties about the use of drugs are clarified, that the effective use of drugs is ensured, and that the impact of reimbursement on budgets is properly managed. A key aim of these agreements is to share the costs of uncertainty between pharmaceutical manufacturers and purchasers (WHO, 2018).

2.4.4. Substitution, generics

If a drug's patent expires, generic substitution is an option, helping to increase efficacy and reduce costs. Generic substitution allows for the use of a drug containing the same API for the same treatment. International Nonproprietary Names (INNs) and generic substitution are regulated differently from country to country and can be divided into three types: mandatory generic substitution, permitted, indicative and non-permitted.

Where generic substitution is mandatory, physicians may prescribe a particular brand, but must give written reasons for the choice. In several countries, it is common practice for pharmacists to inform patients if a cheaper generic product is available (WHO, 2018). Generic drugs as a legal category have been introduced at different times in different countries, from 1984 in the United States (Hornecker, 2009) to 1996 in Italy (Ghislandi et al., 2005).

In the analysis, I focus on generic pharmaceutical markets. Therefore, regarding governmental factors, it is also worthwhile considering how these factors influence (encourage) generic drug purchasing.

Generic substitution:

- Permitted, indicative (Poland, Romania, Hungary, France, United Kingdom)
- Mandatory (Germany, the Netherlands, Italy, Spain)

Prescribing international non-proprietary names (INNs):

- Permitted, indicative (Poland, United Kingdom, Germany, Hungary)
- Mandatory (France, the Netherlands, Italy, Spain, Romania)
- Not allowed (no examples in the nine countries under analysis)

It is worth comparing, using an earlier figure (Figure 8) regarding generic shares by volume, what regulatory incentives are used in the countries with the highest shares of generic drug use (DE, PL, NL, UK) to achieve such high values (subsidy for generic prescription; mandatory generic prescription; generic substitution; mandatory INN prescription).

Several studies have examined attitudes and purchase intentions related to generic drugs (Ferreira et al., 2017; Ganther-Kreling, 2000; Hughes et al. 2002; Sewell et al., 2011; Muzumbar et al., 2013), showing that the level of adoption of generic drugs varies according to the level of need, which is more favourable in less severe conditions (Figueiras et al., 2008). Although understanding attitudes and purchase intentions can provide insights into the wider use of generic medicines, there is little research that helps understand the factors that influence the purchase intentions associated with pharmaceutical products, and the attitudes towards and impact of generic medicines.

Toverud et. al (2015) found that, in general, the more developed a country's healthcare system, the greater the adoption of generic substitutions. In Northern European countries,

the adoption on the grounds of quality of generic products is the highest. It is quite common that almost every survey points out the problem of the lack of information about generic drugs, which inevitably leads to a lack of trust and thus less frequent usage (Toverud et al., 2015).

Policymakers face a lot of challenges implementing policies on manufacturing and marketing generic drugs, but it is important to bear in mind that these policies can result in savings for public health services (Howard et al., 2018; Hassali et al., 2014). It is important to understand attitudes and purchasing intentions and to recognize the factors that may influence the use of generic drugs to appropriately shape future public policy, education, and practice interventions and maximize the use of generic drugs.

While there is well-developed regulation on the use of generic drugs in almost all countries, policies on the pricing and use of biosimilar drugs is still underdeveloped, but this issue is not addressed in this doctoral research.

2.4.5. Pricing policy

Pricing policies are defined as ‘regulations and processes applied by governmental authorities to set drug prices or to exercise price control’ (Vogler-Zimmermann, 2016). They are closely related to reimbursement policies, where drug costs are paid by a third party. The price of a drug is the sum of three elements: the manufacturer's price (the price at which the manufacturer sells it), the distribution margin or mark-up (wholesale and retail), and taxes (i.e., VAT). Price control can be applied at any stage of the distribution chain—for example by controlling manufacturers' prices or regulating distribution margins and mark-ups (OECD, 2020).

Price control applies at different points in the pharmaceutical distribution chain, from the setting of manufacturers’ prices to remuneration caps on wholesalers and pharmacists, and product taxes. The level of details and strictness of this regulation can vary from country to country and even from sector to sector within the same country. In the in-patient sector, direct negotiations between hospitals and manufacturers or wholesalers are usually possible. In contrast, in outpatient care, pricing and distribution margins are more strictly regulated (Panteli et al., 2016).

Thus, drug pricing is an factor intrinsic to competitive advantage, but it is also a rather complex process on which reimbursement policy, regulations and laws created by the government and public authorities have significant influence. Pricing is an activity that

can take several years and accompanies clinical drug development (Dankó-Molnár 2013). Hence, prescribing behaviour is the result of empirical analysis in which the impact of price—pricing constraints—can be detected (Laat et al. 2002). Because of these factors, there is also some regulation and restriction on the supply of available drugs.

Government policy also plays a major role in the development of price levels. The instruments used to shape the price level may include mandatory price reductions for generic drugs relative to the price of the original (i.e., in France the first generic must be priced at least 50% lower than the price of the original; in Hungary at least 40% less), tax rates, and external and internal reference prices.

Medicines are often taxed at a lower VAT rate than other goods or services (see Table 7). Of the countries compared, only Denmark and Germany have general VAT rates for pharmaceuticals (25% and 19% respectively). In France, subsidized drugs are taxed at 2.1% and non-subsidized drugs at 10%. In Sweden and the United Kingdom, prescription drugs are exempt from VAT, while over-the-counter (OTC) drugs are taxed at the standard rates. In Ireland, this distinction is applied between oral and non-oral medicines. In other countries, reduced VAT rate ranges from 4% (Spain) to 10% (Austria, Finland, Italy).

There are three types of drug pricing: traditional (uniform), quantity-based, and value-based. With traditional pricing, a flat (fixed) price is set regardless of volume. When volume-based pricing is applied, a volume discount can be obtained on large volume purchases through negotiation with the financier. Value-based pricing means that different groups of patients may have different access to drugs at a different price, depending on the added value of the therapy for them. See Figure 13.

Figure 13 Three main types of pricing

One of the challenges of value-based pricing arises when the proven benefits of a drug vary significantly between different indications and/or patient subgroups. In such cases, Claxton, Sculpher and Carrol suggest that a uniform price should be set for the drug in question that should be in line with the average of the increase in cost-effectiveness ratios (Claxton et al., 2011).

The reference pricing system (RPS) is the approach that strongly determines drug pricing in Europe. RPS is a drug pricing policy through which interchangeable drugs are grouped into a reference class, often based on the same API (anatomical therapeutic chemical [ATC] classification level 5) or on a chemically related subclass (ATC level 4). Most countries set the reference price at the retail pharmacy price of the lowest priced drug in the reference group. The financier determines the price (the so-called 'reference price') to be reimbursed for all the drugs in the group. If the retail pharmacy price of the drug exceeds the reference price, the patient must pay the difference in addition to any other applicable deductibles (such as prescription charges or a percentage of co-payment). RPS can encourage the diffusion of generic drugs and promote competition in pharmaceutical markets. The more generic and other lower-priced substitutes of an equivalent efficacy are available in the same market at a given time, the more viable the system becomes. Obviously, this system can only be applied in markets with therapeutic alternatives (i.e., generic medicines) (WHO, 2018).

There is a distinction between external and internal reference pricing. Internal reference pricing means that more expensive drugs in the same reference group can only receive the reference reimbursement, thus competition in the national pharmaceutical market is encouraged. An external price reference is another key pricing mechanism often used in the outpatient sector. In this case, drug prices are set by comparing them with prices in selected reference countries. This reference price can be used to set or negotiate the price of a product in that country. Several countries (including Austria, Belgium, Estonia, and Romania) use the external price reference as a starting point to determine the list price of certain drugs (typically new patented drugs). The second step involves negotiations between the financing party and the pharmaceutical manufacturer about the specific reimbursement price and conditions. (OECD, 2020)

Manufacturer prices are subject to legal or regulatory requirements in most European countries. The so-called 'free pricing' countries, such as Denmark, Germany, and the UK, belong to the minority. Even when manufacturers are free to set their prices, they are influenced by indirect measures (such as internal reference prices, parallel imports,

legally enforced discounts and rebates, and individual contractual agreements between payers and manufacturers). In Germany, free pricing has been restricted following the introduction of the AMNOG regulation in 2011: for the market entry of drugs with a new API or indication extension, free pricing is only valid for the first year after marketing authorization. Thereafter, only an agreed reimbursement is paid for drugs with proven added therapeutic benefits (both for patients with statutory and private insurance), while the maximum reimbursement is defined based on internal reference prices (Panteli et al., 2016). See Table 6.

Table 6 Review of relevant pricing strategies, 2016 (Panteli et al., 2016)

Country	Free pricing	External reference pricing	Internal reference pricing	Value-based pricing	Other
UK	YES (see last column)	NO	NO	For certain products	Negotiations, profit margin (PPRS)
FR	NO	YES (ASMR I, II and III)	YES	NO	Negotiations
DE	YES (AMNOG)	YES (as a secondary criterion used as a basis for negotiation in price negotiations)	YES	YES (AMNOG)	
IT	NO	YES	YES	YES	Negotiations (performance-based)
NL	NO	YES	YES	NO	Negotiations (for costly medicines)
PL	NO	YES	YES	YES	Negotiations
ES	NO	YES	YES	NO	

Kanavos et al., from a study of the US, Canadian, and the top five EU markets, concluded that although reference pricing increased generic penetration, due to the artificial price ceiling no real price competition evolved, thus the use of generics tended to reduce prices less significantly (Kanavos et al., 2008). However, the economic crisis of the 2000s has made it increasingly important to reduce pharmaceutical expenditure in a growing number of countries, thus health policies that encourage generic drug prescription are increasingly being implemented (Belloni et al., 2016).

As patents expire and generic alternatives become available on the market, RPS are frequently revised in most of the countries under study. The frequency of reference groups and price reviews varies from country to country, from biweekly (Denmark) and quarterly (Finland) to every five years (France). Reference groups and prices are updated quarterly in Estonia, Germany, Hungary, Portugal, and Slovakia. Slovenia updates them every six

months, while Italy updates more frequently (on a monthly basis). Greece reviews prices twice a year (WHO, 2018).

Many countries have established close links between pricing and the reimbursement process. In Finland and Sweden, for example, drug pricing and reimbursement are done concurrently. In other countries (such as Italy and Portugal), the same institution is responsible for both pricing and reimbursement (WHO, 2018). Since pharmaceutical policy instruments together determine the market patterns in each country, I have tried to summarize the pharmaceutical policy instruments for the nine countries surveyed in the table below. It is essential to consider the specific pharmaceutical policy regime in each country when results are analysed. See Table 7.

Table 7 Supply and demand side of pharmaceutical policy in nine countries, 2017 (author's editing) (Source: Barbu, 2012; Dylst et al., 2012; Kaplan et al., 2012; Kanavos et al.; 2014a, 2014b; Panteli et al., 2016; Thomson-Mossialos 2010; Vogler, 2012; Vogler et al., 2015); WHO, 2018)

		UK	DE	NL	FR	IT	ES	HU	RO	PL
Demand side	Reimbursement for generic drug prescription	x	x					x		x
	Mandatory INN prescription			x	x	x	x		x	
	Reimbursement for substitution of generic medicines	x			x			x	x	x
	Mandatory substitution		x	x		x	x			
	Officially defined retail and wholesale margins		x	x	x	x	x	x	x	x
	Authorized discounts and volume agreements	x	x		x	x	x	x	x	x
	Clinical guidelines	x	x	x	x	x	x	x	x	x
	Reimbursement system	x	x	x	x	x	x	x	x	x
Supply side	External reference prices		x	x	x	x	x	x	x	x
	Internal reference prices		x	x	x	x	x	x	x	x
	VAT on drugs (standard rate) (%)	0 (20)	19 (19)	6 (21)	2/10 (20)	10 (22)	4 (21)	5 (27)	9 (20)	8 (23)
	General price depends on the price of the innovator	-	-	-	50%	min 20%	-	20-50%	-	20-50%

2.5. Influence of pharmaceutical marketing tools

To meet customer needs in the pharmaceutical industry, marketing tools have to be used in a specific way. As described in the previous chapters, even the definition of the customer poses difficulties, since different interest groups need to be satisfied with the same product (patients, physicians, and public actors as financiers and authorizing

bodies). The complexity of designing product attributes and product positioning cannot be compared to that of any other industry. The first step is to define the unmet needs of the consumer—i.e., the patient—and then to set up an appropriate product strategy (Szabóné Streit, 1999). In an article (Stros-Lee, 2015), Stros and Lee point out that the order of market entry can have a critical impact on the sector's output, as both early and late strategies can be effective. Not only is product policy of great importance, but also marketing communication and pricing. Distribution issues are less relevant for this thesis.

2.5.1. Product attributes—with particular emphasis on the role of clinical evidence (Product)

Prescription drug purchases are based on real needs, not on consumer desires. Drugs are products which require marketing consideration and, moreover, the considerations of final consumers—in the absence of professional knowledge—cannot be incorporated without the help of physicians as agents. The quality of drugs from the perspective of both physicians and patients can be understood along the lines of experience and trust, and the role of search criteria is negligible (Bauer et al.; 2014). In the complex process of prescribing, clinical appropriateness is the first consideration in the decision of physicians (Campo et al., 2005, Furberg et al., 2010).

Crawford and Schum, in their study on anti-ulcer drug prescription, concluded that patients were fundamentally risk averse, and that initial uncertainty about medication quickly declined, so they were not interested in switching drugs—i.e., they preferred to continue therapy with the drug of first choice. Authors also point out that this is why marketing activities that create a strong positive perception for consumers can lead to market concentration, even if alternatives that are available are essentially indistinguishable (Crawford-Shum, 2005). Further, when a sufficiently large initial patient base is formed, as an externality the market share of a given product or brand may continue to increase since its widespread use suggests that it is a generally accepted procedure, creating the impression that it has clinically beneficial properties (Berndt et al., 2003).

The process of drug purchase is thus permeated by trust, a key factor in relational commitment. To build loyalty, trust must first be earned (Sirdeshmukh et al., 2002). Satisfaction, and the resulting consumer trust, help to retain consumers, which in the case of pharmaceuticals must be developed both for physicians and patients. Consumer trust is an important measure of loyalty. Consumer retention is influenced by other factors as

well, such as switching costs, which can make it more difficult, costly, or impossible for consumers to switch between products (Fornell, 1992; Jones et al., 2000). If trust in the original product has been earned, this creates a barrier to switching to a generic product.

Vertical product differentiation is theoretically feasible at the level of the active ingredient based on the clinical properties of the product, but in practice it is not easy to achieve, even for doctors, due to the uncertainty related to the assessment of product quality. In many cases, product differentiation based on other attributes (horizontal differentiation) is of great importance (Laat et al. 2002).

The most important of these product attributes is the clinically meaningful efficacy and safety of the medicinal product. In the literature, Azoulay was the first to discuss the relationship between the scientific value of a drug and drug sales (as highlighted in the author's work) (Azoulay, 2002). In a study that investigated the market for H2 antagonists, Azoulay concludes that the role of marketing (communication) has a much more dominant effect on the demand for drugs than their scientifically proven appropriateness. Nevertheless, the latter effect can be considered statistically and economically significant. A close reading of the article reveals that the author did not investigate the impact of marketing communication on clinical appropriateness (i.e., the effect of detailing is performed with a clinically preferable drug). Clinical appropriateness can be reflected in the sale (prescribing) of drugs in this way too, although indirectly. Azoulay's study concludes that in the market for H2 antagonists, Zantac was able to outperform Tagamet because of its better clinical profile.

A study by Berndt et al. on antidepressants suggests that products supported by new scientific evidence are followed by an increase in marketing activity. A sales increase is attributed both to scientific evidence and the decrease in price, and a relatively more favourable side-effect profile is a more significant factor in the increase in market share than efficacy. At the same time, the authors note that the order in which drugs enter the market also has an impact on their sales (Berndt et al., 2002). However, the order of market entry does not necessarily determine sales performance, as a better product can 'make up' for any disadvantages even if it enters the market later (Fischer et al., 2010).

Below are listed some further examples of when a clinically superior compound has become dominant in the market:

- Lipitor, for many years the world's biggest blockbuster for a long time, has been widely communicated by its manufacturer (Warner-Lambert) as being as effective

at lowering cholesterol as its competitors (Merck: Zocor, Bristol Myers-Squibb: Pravachol) but at a much lower dosage. (Winslow, 2000)

- An interesting example in the ACE inhibitor market, and also in the context of subsequent research, is the case of Vasotec (enalapril) and Capoten (captopril). Enalapril entered the market later than captopril, yet it managed to obtain a much larger share of the US market. The main reason for this was Merck's successful marketing efforts based Enalapril's superior product attributes (Werth, 2013).
- The examples of Zoloft and Prozac are also interesting. In the antidepressant market, Zoloft (originally in second place) was able to overtake Prozac without being able to provide a convincing argument that the product is associated with a real advantage, the two compounds being clinically very similar, so it must have been the effectiveness of the marketing activity that led to this result (Cutler-Berndt, 2007).

To underline the importance of a side-effect profile, a study published in the United States in July 2002 demonstrated the cardiovascular-risk-increasing effect of hormone therapy for women. Following its publication, the prescribing of this type of drugs began to decline steadily, achieving 66% and 33% respectively for the two most popular products after one year, supporting the importance of clinical evidence about the side-effect profile on prescribing (Hersh et al., 2004).

In a survey of US hospitals by Schumock et al., it was revealed that physicians mentioned efficacy, safety, and personal experience as the most important factors in drug prescription, with FDA-approved indications and drug prices considered less important factors (Schumock et al., 2004).

Girdharwal and Singh reached a similar conclusion. On a 10-point scale, physicians were asked to rate what influences them when prescribing a drug. The top five factors were product quality (9.89), product price (8.50), product availability (8.46), the image of the company (8.37), and regular visits by sales representatives (8.20) (Girdharwal-Singh (2007).

Last but not least, the role of marketing efforts is to ensure that services are also provided at a high level after sales, thereby strengthening the relationship between consumers and the pharmaceutical company, thus ensuring that consumers will also choose the company's product next time (Szabóné Streit, 1999).

In terms of market segmentation, it is recommended to segment consumers according to the diseases and therapies liable to be used. It is essential to bear in mind that decision-making does not solely involve consumer choice. It is important to distinguish between the market for over-the-counter (OTC) and prescription-only (Rx) drugs that are subject to different regulations (Blaskó, 2011).

2.5.2. Price

As explained in the chapter on pharmaceutical policy instruments, a significant proportion of drug expenditure, in particular in relation to the hypertension drugs under research, is covered centrally by public funds in the form of reimbursement. Therefore, the consideration of the real cost of drugs is unique to the pharmaceutical industry. Patients pay a fraction of the price of the drug, and price is not necessarily the primary determinant of the decision of the prescribing physician. Thus, the prices for the drugs in the studied class are mainly determined by the financier, who is only indirectly involved in purchasing decisions. Each country uses different regulatory mechanisms to control pharmaceutical expenditure and to ensure the quality and efficacy of drug therapies. Overall, the observed differences in drug costs should be interpreted in the context of the differences in volume and structure of consumption and price levels, as well as waivers and their impact on drug costs (Panteli et al., 2016).

'Price is the value denoted in money (maybe in other form of compensation) that the buyer pays for a product' (Rekettye, 2011). In the pharmaceutical sector, prices are determined by pharmaceutical policies and regulations, as well as by the pricing policies of companies. By pricing policy, we refer here to company pricing policies, which are related to the various functions of companies and significantly influenced by the environment in which they operate. The pricing policy of a company is determined by the market conditions under which the company operates. The main market types can be clearly defined using four variables (Rekettye, 2011):

- Number of companies in the market
- Constraints on market entry
- Differentiability of the product
- Typical forms of competition

On this basis, a distinction can be made between monopolistic competition in the pharmaceutical sector and perfect competition in the generic sector. The market for biosimilar and more complex generic products is different, into which fewer companies

can enter with their products (oligopolistic market). In the originator market, legal barriers to market entry are constructed in the form of patents, as discussed before. Even in this case, companies are not completely free to set any price they want. Prices should be set in such a way that the demand for the product satisfies the profit ambitions of the company.

The pricing of innovative drugs can be divided into two stages: strategic and operational price management. Strategic price management covers the period until product launch, and is then followed by operational price management. Due to the high intellectual added value of innovative drugs, manufacturers tend to set prices well above the marginal cost of production to recover the costs of both successful and unsuccessful developments, and to make a profit. This is where patent and licensing issues, already discussed earlier (Kaló, 2010), come into play. In a study, Kaló describes how the price of a product should in no way be higher than the real value of the therapy. In the latter case, the product will certainly not be included on the list of reimbursed products and demand will fall to the minimum. When a decision is made about pricing for an original drug, the real value of the therapy must first be estimated.

The drug price is generally constructed as follows:

(Producer price + wholesale margin + retail margin) + VAT = consumer price

Consumer price – reimbursement = prescription charge paid by the patient

As for generic drugs, pricing is most affected by the pharmaceutical policy instruments described earlier. The most important of them are the mandatory price reduction (in Hungary, at least 40% for the first generic) and the institution of reference pricing. The use of generic drugs is approved as a cost-saving mechanism in all the countries under study, with varying degrees of intensity. Generic substitution is an option in almost all countries in the sample (except for in Austria), while compulsory in others (i.e., Denmark, Finland, the Netherlands, Sweden). In France, generic substitution is encouraged both by a system of performance fees for physicians and by higher profit margins or additional payments to pharmacists. Generic drugs are almost invariably cheaper than innovative products. The price of generic products is significantly affected by the number of competitors. Patients can usually refuse substitution, but then they are expected to pay the price difference at their own expense (Panteli et al., 2016).

As for the approval of subsidies for combined drugs (several APIs in one formulation), practices are different in European regulations. In Hungary, for example, the National

Health Insurance Fund Management has a policy that if a company produces mono-component equivalents of a combination product (each API in a separate formulation), they use the sum of the consumer price of these mono-component products as the maximum consumer price. If the manufacturer does not have such a formulation, then the sum of the lowest mono-component products available on the market is applied. The use of combinations is a common practice for antihypertensive drugs, and it is therefore necessary to pay attention to this effect in the analysis.

2.5.3. Distribution system (Place)

Medicines are sold through wholesalers and pharmacies, and hospitals are dominant users, too. In terms of the sale of prescription medicines, distribution is not a major issue for this research. The reasons for this—and hence the discussion of this topic—will be discussed in more detail in Chapter 2.7 on pharmacists' prescribing rights.

2.5.4. Marketing communication (Promotion)

In the prescription-only market, the most important marketing communication tools are personal selling (detailing), sales promotions, and public relations. Advertising in the classical sense is not an option, as this is prohibited by law, as set out in the Code of Ethics for Pharmaceutical Communication (Blaskó 2011).

The information gap between physicians and the pharmaceutical industry can be wide, especially for new medicines. For doctors, it takes considerable time and effort to keep up with technological innovations and the range of new products. The pharmaceutical industry has the task of bridging this gap and making their products known to the market (Laat et al. 2002).

Through the visits of medical representatives and attending symposia, doctors acquire a large amount of information on the clinical appropriateness of medicines (Gönül et al., 2001), and these activities have important informative (reducing cognitive uncertainty) and persuasive (positive impact on prescribing) effects (Narayanan et al., 2005).

Concerns have been raised about the quality of information provided by the pharmaceutical industry in their marketing activities (Othman et al., 2009; Heimans et al., 2010; Villanueva et al., 2003), and there is also evidence that physicians tend to be critical of industry activities, either in the scientific literature (Kesselheim et al., 2012) or among peers (Fickweiler et al., 2017). Nevertheless, promotional activity is certainly one of the most important factors in sales decisions about drugs. Several studies have indicated that

marketing activities tend to have a detrimental effect on the quality of prescriptions and increase demand for drugs, while other studies found no significant correlation between these factors. Spurling et al., after reviewing the relevant literature, could only conclude that there is no evidence that marketing communication improves prescribing habits (Spurling et al., 2010). It is interesting for this thesis that Greving et al. found that, in relation to antihypertensive drugs, among Dutch physicians in the early 2000s (when there were no generic products in the API class), physicians who relied more on pharmaceutical information were more likely to start prescribing ARBs to their patients (Greving et al., 2006).

Some literature deals with how various types of information about various drug attributes can affect the sales of drugs. Azoulay's research into the US market for histamine H2 receptor antagonists concluded that the marketing activities of a typical manufacturer have a greater impact on drug sales than scientific results (Azoulay, 2002). However, the role of the latter is not to be neglected: the conclusion was that comparison with placebo or other drugs from another class with a different API led to an increase in the whole market for the class, whereas comparison of a drug with others in the same class of APIs led to an increase in the market share of the drug within the class. Naturally, these results are incorporated into marketing communication activities. In line with this, according to Venkataraman and Stremersch, the effectiveness of marketing activities is modulated by the efficacy-related characteristics or side effects of the drug (Venkataraman-Stremersch, 2007). The picture is further complicated by the fact that it does not seem to matter what information is made available to physicians at each stage of the product life cycle, because in a competitive environment, emphasizing certain attributes can be both beneficial or harmful to the sales of the product (Kappe-Stremersch, 2016).

Looking at the impact of marketing investments more generally, Berndt et al. produce several findings from an examination of the market for anti-ulcer drugs. Marketing investments clearly have a positive effect on the sales of drugs, but this effect clearly spills over from the original product to the generic products that follow. It is mentioned that switching between therapies takes less time in cases when the manufacturer can demonstrate real added value (i.e., lower dosage, fewer side effects) (Berndt et al., 1996).

Having discussed the general characteristics of marketing communication, the next step is to consider the marketing communication tools used by pharmaceutical manufacturers.

2.5.4.1. Pharmaceutical representatives

Representatives of pharmaceutical companies provide detailed information to professionals and physicians about a product or a group of products of the company. Drug detailing creates an opportunity to present new scientific findings and technological innovations. Pharmaceutical representatives can draw attention to new drugs, and to information and experience with a new product. Due to time constraints they typically give short, concise presentations that highlight the specific product attributes that distinguish their own products from others on the market. They can also provide detailed written material, small gifts (usually marked with the name of the product), and product samples. During detailing, the sales representative may invite the physician to attend various marketing communication events, symposia, or post-marketing activities, and to participate in research. Such detailing usually lasts 10–20 minutes, but some physicians refuse or limit the number of such visits (Laat et al., 2002).

Gallan's research concluded that three quarters of physicians found the information they received from sales representatives of pharmaceutical companies to be very useful or fairly useful. Eighty percent of them believed that the information they receive is very accurate or fairly accurate (Gallan, 2004). However, according to Lieb's research, only 43% of physicians think they receive adequate and accurate information from their sales representatives (Lieb-Scheurich, 2014).

In a study, Campo sought to identify whether detailing and drug samples increase physicians' price sensitivity to competitors' products. The research revealed that while most physicians received product samples during the visits, they were less aware of the prices of those products. Physicians preferred to receive directly applicable information and facts. They preferred verbal to written information. Taking these facors into account, prescribing habits changed positively during detailing (Campo et al., 2005).

2.5.4.2. Opinion leaders

Opinion leaders are acknowledged persons in their profession, experts, and physicians whose job is to deliver lectures, seminars, symposia, or marketing communication presentations at various training courses and events such as conferences. Opinion leaders present a favourable image of particular drugs made by the companies that support them. Therefore, it is important that the audience is aware of such links between the speaker and the companies concerned (Laat et al., 2002).

The perception of a newly introduced drug largely depends on who and what is said about the product; in this, particularly important is the role of pharmaceutical industry and physicians working in hospitals in shaping opinions. For the latter, clinical experience is of paramount importance in relation to the adoption a new drug in medical practice (Prosser et al., 2003).

In an article, Stros questions the actual impact of opinion leaders as opposed to other marketing communication tools such as the impact of sales representatives (Stros-Lee, 2015).

2.5.4.3. Marketing communication events

Marketing communication presentations are short lectures delivered by representatives of pharmaceutical companies to which physicians are invited. Such courses and conferences provide a good opportunity to influence physicians. Such a means of influence may be a well-chosen and well-known opinion leader—whose opinion is respected (including by the company)—and a presentation about the product of the company. Furthermore, conferences provide a platform for physicians to talk to experts, opinion leaders, and persons with greater expertise on the subject, and to discuss topics in more detail. They have the opportunity to discuss the use of specific therapies informally. An exchange of information in a live setting can change prescribing habits and the choice of medication (Campo et al., 2005).

Research by Campo et al. revealed that gifts and sponsoring conferences, while not having a large direct effect on choice of drugs, can increase physicians' commitment to companies. Apart from this, gifts are seen by most physicians as ‘relationship gifts’ that are appreciated and expected, and these marketing tools enhance brand loyalty in the long run (Campo et al., 2005). However, Prosser et al., in an article about written information as a means of transmitting information of limited importance, highlighted the importance of local guidelines (Prosser et al., 2003).

2.5.4.4. Drug samples

Drug samples are one of the most recognized benefits among physicians. In their research, Lieb and Scheurich found that 69% of physicians accepted free drug samples from their sales representatives (Lieb-Scheurich, 2014).

Free drug samples offered during detailing are necessary so that physicians, while forming their opinions, will remember the drug in question or perhaps update their

knowledge about a new or a less known product (Campo et al., 2005). The authors found that physicians appreciated free drug samples but did not strengthen their commitment to companies. They believe that the frequency of sample distribution may be the main reason for this. Physicians find that samples are useful gifts, partly as a way of informing patients of the form in which they can buy the product, and partly for use in emergencies. Samples can help to build brand awareness. Among the factors influencing drug prescription, this one appears to be less influential (Campo et al., 2005).

2.5.4.5. Branding

Brand building is one of the most important tools in the toolbox of marketing activities of pharmaceutical companies to increase the brand value of their drugs both to physicians and patients.

While the impact of marketing activities cannot always be measured precisely, branding and brand building is one of the tools that is most likely to pay off. Brand equity is the added value that products and services are attributed, and can also be manifested in how consumers think, act, and feel about a brand, prices, market share, and brand profitability (Kotler - Keller, 2012; Laat et al., 2002).

Those consumers who recognize a brand are more likely to buy the related products than those who are do not (Sanyal-Datta, 2011). For me-too products (those drugs whose APIs are structurally very similar, act according to the same mechanism, are therapeutically equivalent, and have similar side-effect profiles and efficacy), differentiation from competitors is a crucial strategic issue, and the ideal way to do this on the market is through branding, creating strong brand equity (Szabóné Streit, 1999).

Brand equity facilitates the acceptance of new products and contributes to proper distribution and represents the position of the product on the market in the eyes of consumers. Brands associated with strong brand awareness are present in consumers' associative memory and when a need for a therapy or product arises, consumers are more likely to remember to choose from them. Over time, a positive brand attitude develops a strong emotional attachment beyond brand preference (Sanyal-Datta, 2011).

Campo's research revealed that physicians still prefer brands with a long tradition, as more money is assumed to have been spent on R&D in the development and production process of the product, suggesting that product safety and efficacy may be higher (Campo et al., 2005).

The use of a well-promoted brand name becomes a crucial element in marketing communication activities during detailing. As for prescription-only, therapeutically equivalent drugs, branding is an important factor in building repeat purchase and product loyalty when drugs are chosen by professionals. Research results reveal that direct marketing to doctors (drug detailing, conferences) can have a strong influence, which in turn may explain the impact of brand names on the prescribing habits of practitioners (Ward et al., 2008).

Drug detailing increases learning, thereby supporting brand convergence among physicians, which in turn leads to increased brand choice in drug prescription. In a study in Yemen, a significant effect of drug detailing and marketing communication was not detected, but authors found a link suggesting that branding significantly and positively influences physicians' prescribing behaviour (Mohsen-Zurina, 2018).

Burmann and Kanitz point out that, currently, the pharmaceutical landscape is changing. This needs to be addressed in such a way that brand architecture is the most important first step in ensuring that pharmaceutical companies adopt a customer-orientated rather than a product-oriented business approach. Consequently, this approach may help achieve commercial success in the future (Kanitz-Burmann, 2012).

Nevertheless, research by Leeflang and Wieringa showed that the use of marketing communication tools is brand specific and that most standardized models are not uniformly applicable in real-life situations. Their study was carried out in the Netherlands, where they found that marketing expenditure had little or no effect on the demand for prescription drugs (Leeflang-Wieringa, 2010). It is important to note that branding may primarily have an impact at the level of brands, while effects at the level of APIs may be indirect.

2.5.4.6. Country-of-origin effect

Prescription drugs have a strong national character, despite the highly international nature of the industry. This can be explained by the fact that demand is also affected by social and cultural differences between countries. There are national differences in the provision of universal healthcare and insurance, hence specific national patterns can be observed (Laat et al., 2002).

The image of the country of origin is likely to influence brand equity have an impact—i.e., on the strength of the brand, hence brand awareness. According to Sanyal, country

of origin and product quality are two interrelated concepts. When consumers do not actually use a product, they can only estimate its quality, and one of the bases for such predictions is the country of origin. It has been demonstrated that for products made in countries with a lower prestige, the location of the country of production can have a significant negative impact on brand perception. As a consequence, the willingness to prescribe will also be lower for these products. Studies have shown that country of origin has a strongly positive effect on brand strength and brand awareness (Sanyal-Datta, 2011).

Bahrinizadeh et al. also found that country of origin has a positive impact on brand equity through brand awareness, brand building, and brand loyalty. They point out that, in their view, pharmaceutical marketing should pay close attention to the country-of-origin effect, as this can increase the brand equity of drugs. Despite a strongly globalized world economy, the country of origin is still a determining factor (Bahrinizadeh et al., 2014).

An article that summarized a study on the marketing strategy of ACE inhibitors in the early 1990s revealed that Servier's perindopril (Coversyl) also influenced national preferences among French prescribers. The manufacturers of 14 ACE inhibitors that were still on the branded market at the time attempted to distinguish themselves from the rest of the group with various messages: older drugs (captopril, enalapril) mainly emphasized their use in new indications (heart failure, post myocardial infarction, diabetes-related hypertension), while later entrants (i.e., ramipril, perindopril, quinapril) focused on the preventive effect on organ damage, and recent entrants (trandolapril, benazepril) attempted to build their communication more on aspects of convenience. In addition to these factors, the effect of country of origin arises as a differentiating factor (Peny, 1994).

2.6. Factors influencing physicians' choice of medication

The sales of prescription drugs are largely defined by the number of prescriptions physicians write (prescription), and on whether patients follow the prescription (patient cooperation), and which products are dispensed to patients in pharmacies and hospitals in exchange for the prescription.

It can be said that the market performance of therapies is mostly determined by physicians’ decisions. To maximize market performance and to select the right branding strategy, it is essential for manufacturers to understand the factors that are most likely to influence medical decisions. It is important to obtain a complex picture of what drives

physicians' decision in each therapeutic situation, what factors influence their perception, and which industry players can influence their therapeutic decisions significantly.

2.6.1. The decision-theoretical background of drug prescription

Correct and accurate prescription is of great importance for health services as the inappropriate prescription of a drug can have clinical, financial, and even legal consequences.

Both Hogerzeil (Hogerzeil, 1995) and Carthy et al. (Carthy et al., 2000) demonstrated that physicians occasionally prescribe unnecessary or inappropriate drugs, and additionally that unhelpful prescription and misuse also occur. All these can decrease the quality of care provided to patients, and thus increase the cost of healthcare (Ahmed et al., 2016).

Empirical research can rarely provide solutions to such anomalies, which is why theoretical approaches become important when analysing physicians' decision-making processes (Theodorou et al., 2009).

Theories of individual behaviour can also be applied to drug prescription, as most decisions in clinical practice are individual in nature (Godin et al., 2008). Thus, it is true that in real situations reactions to external stimuli occur: physicians' and pharmacists' behaviour and intentions can be predicted on the basis of cognitive theories (Eccles et al., 2006). Sheeran's study found that intentions explain 28% of behaviour (Sheeran, 2002).

However, the behaviour of physicians is a much more complex phenomenon, and to analyse physicians' actions it is necessary to understand the social context of the whole process, the expectations patients have of drug prescription, and the extent to which patients are willing to accept a prescribed treatment.

2.6.1.1. Theoretical approaches

The theories listed below can help understand the mechanisms of decision making and thus shed light on the drivers of physicians' behaviour.

- Agency theory

  This theory suggests that one party (physician) acts for another party (patient) on behalf of a third party (a pharmaceutical manufacturer). According to this theory, the marketing activities of pharmaceutical companies are aimed at providing physicians with the right information to encourage them to choose the company's

products when prescribing drugs. Various environmental elements are thus relegated to the background (Groves, 2006.)

- Persuasion theory

  In the case of persuasion, effective communication is used by one party (sales representatives of the pharmaceutical company) to influence the decision-making process of the other party (physicians). This has four elements: information from the sender (sales representatives of the pharmaceutical company), the physician (buyer), exchange between the receiver and the sender (sales representative and physician), and the change in behavior (physician's prescribing behaviour).

  According to O'keefe (O'keefe, 2002) and Petty and Cacioppo (Petty-Cacioppo, 1986), factors influencing physician prescribing behaviour include personal contact with the sales representatives of the pharmaceutical company, environmental stimuli (attitude of patient and sales representative), marketing communication, sales promotion, drug-related information (price, dosage, mechanism of action, allergens, etc.), and physicians' opinion about a drug.

- Theory of buyer behaviour – stimulus-response (SR) theory

  Both buying behaviour models, such as the stimulus-response (SR) model, show that individuals are influenced by emotions and knowledge. Xing and Othman (2015) concluded that the SR model does not focus on the process, but rather on stimuli and consequences. Through marketing mix elements, pharmaceutical manufacturers generate various stimuli that influence physicians' intention to prescribe a drug; these stimuli penetrate physicians' perceptions and ultimately transform them into effects (Xing-Othman, 2015).

- Theory of planned behaviour (TPB)

  According to Eccles et al., the theory of planned behaviour (TPB) is the most appropriate and commonly used method for understanding physicians' responsible prescribing behaviour (Eccles et al., 2012).

  The extent to which physicians are willing to prescribe a particular drug depends largely on their attitude towards marketing activities and other factors such as the availability of drug-related information, sales incentives, the quality of sales representatives' work, and the brand name of the product (Murshid-Mohaidin, 2017).

  The second component of the theory measures the strength of patients' demand for a particular drug, patients' expectations, professional information provided by pharmacists, and collaboration between pharmacists and physicians. Ajzen (1991)

points out that the theory suggests that individuals are rational agents who process information that leads to behavioural intentions, and then to actions. For example, if physicians are convinced that a drug could bring about positive change in patients' condition and intend to treat patients, then their attitude towards a particular drug can be positive. Patients have expectations before they even see a physician; physicians meet these expectations in the form of often unclear questions. One of the tasks of physicians is to formulate patients' requests in precise terms and to find the best solution they can. Prescribing may also involve situations when patients try to put pressure on physicians to obtain a prescription, they consider important (Virji-Britten, 1991). Obviously, the prescribing process cannot be simplified to physicians and patients; it takes place in a social context and is influenced by many other factors. The third factor of TPB theory deals with behaviour based on experience and product knowledge, focusing on future problems.

- The Theory of Social Power (TSP)
  Regarding prescribing decisions, power is expressed as the ability to influence. Social power is the ability to influence the behaviour of someone else through persuasion, which in the health context refers to the role of individuals to exert significant influence on those affected to change their behaviour (Basak et al., 2015). Expert power, however, refers to the knowledge of individuals (in this case, expert opinions) who can draw on their experience and skills to influence physicians' prescribing intentions, highlighting the relevance of the pharmacist–physician interaction (Rigby, 2010).

2.6.1.2. Sources of error in the prescribing process and recommended corrections

Sources of error can arise from insufficient information for doctors (not being aware of the latest pharmacological findings, ignoring the cost elements of medicines, giving in to pressure from the patient, subjective judgements about research findings about medicines and experience, or treating problems with medication for which there is no proven medical solution).

The World Health Organization supports a six-step approach to minimizing the number of incorrect prescriptions, to which Pollock et al. (2007) added two additional points (7 and 8). These are the following, which also define the steps in the prescribing process:

1. Assessment and clear definition of patient's problem.
2. Definition of the therapeutic goal.
3. Choice of an appropriate drug therapy.
4. Physicians should develop their personal prescribing practices. Detailed guidance on how to develop this can be found in the WHO manual (De Vries et al., 1994), and the STEPS framework (Safety, Tolerability, Effectiveness, Price, Simplicity) can also help with building a formulary.
5. Physicians should start therapy in awareness of the relevant details and should consider non-pharmacological therapies as well.
6. Physicians should provide an appropriate level of information, give precise instructions and warnings; and
7. should regularly evaluate the therapy (i.e., monitor the results of the treatment, and consider discontinuing the medication if necessary)

   This is particularly important in the light of research by Shaughnessy (2003), who pointed out that physicians often fail to consider costs to be an important factor in prescribing (Shaughnessy, 2003).
8. Use of computers and other tools to reduce prescribing errors.

   To apply the first seven guidelines with maximum effectiveness, it is essential to have a working knowledge of current drugs and an understanding of emerging drugs. There is now a wealth of software applications that can help doctors do this (Rotschild et al., 2002., Clauson et al. 2004).

2.6.2. Range of products considered by physicians, and factors determining the medical acceptance of new pharmaceutical therapies

As described above, physicians are the intermediaries between patients and therapies on the market. Physicians are expected to give the best possible advice to the best of their knowledge (Laat et al., 2002). Warayuanti and Suyanto (Warayuanti-Suyanto, 2015) showed that purchase attitude is based on how future purchase behaviour is defined. In this context, purchase attitude includes confidence in the product and knowledge about the consumer's purchasing power (Madahi-Sukati, 2012).

In their research aimed at understanding the prescribing behaviour process, Campo et al. found that the decision-making process is typically influenced by a variety of factors, each of which captures (clusters) several different effects (Campo et al., 2005). The main effects can be divided into four groups, which are:

- multi-actor setting, in which the physician is the main decision maker and not the patient,
- prescribing strives to achieve multiple goals,
- multiple sources of information, leading to information overload,
- multiple sources of diagnostic and therapeutic uncertainty

In the context of specific therapeutic options and API selection, Denig attributes a decisive role to the number of drugs that come to the mind of physicians during their decision-making process (the evoked set). According to the model, physicians choose to prescribe a drug either out of habit or when actively searching for a solution to a clinical question. The effect of the decision feeds back into the decision-making process and is incorporated into the experience and knowledge set—which underlies future therapeutic choice—and drug selection habits. Studies have shown that the size of the 'evoked set' among Dutch hospital physicians in the 1990s averaged between 1.7 (antiaggregant drugs) and 5 (antihypertensives) drugs, depending on the drug class (Denig, 1994). In turn, information from the environment, such as training, information on clinical trials, or marketing communication from pharmaceutical companies, affects the emerging alternatives in the 'evoked set' and the knowledge of therapeutic options. A study carried out among Dutch general practitioners revealed that GPs prescribed an average of 233 different drugs over a year, accounting for 31% of the drugs on the market. There seems to be a considerable difference between groups of physicians. Physicians who prescribe the least drugs use on average 111 (15%) drugs, while physicians that prescribe the most use on average 353 (47%) different drugs. More types of drugs were prescribed by physicians who had more or highly qualified patients, and in rural practices that also dispense drugs. This is also true of practices that prescribe more drugs in terms of total volume and have more frequent visits or use pharmaceutical information resources more frequently (de Bakker et al., 2007). In relation to prescribing patterns within drug classes, a US study found that for 80% of drug therapy classes, most physicians prescribed at least three types of drugs. However, in two drug classes for which generics were typically prescribed (for opiates and ACE inhibitors), about half of the physicians prescribed only one or two drugs. Regardless of the therapeutic class, it has been found that physicians who choose from a narrower repertoire tend to prescribe heavily promoted drugs (Joyce et al., 2011).

The branch of medicine in which physicians work also influences their choice of medication. Donohue et al., in their analysis of prescription data on antipsychotics in the US, found that psychiatrists prescribe more APIs of antipsychotics than those in other fields. This was explained by the fact that psychiatrists tend to focus on a narrower therapeutic field and presumably care for psychiatric patients afflicted by illness of a different severity. Furthermore, it was also observed that over five years there has been a significant change in terms of which API physicians preferred to prescribe. The change in preference was partly attributed to the new clinical data reported in the research period, and to the off-label prescription of certain drugs; furthermore, it was also suggested that physicians either were not aware of or did not care about the fact that less frequently prescribed older drugs were cost-efficient, while newer drugs were heavily promoted by manufacturers (Donohue et al., 2014). Hospitals exerted more significant influence on prescription through professional guidelines, restrictions, and clinical formularies (Schumock et al., 2004).

There are also examples of geographical differences even within the same country. Melamed and Rzhetsky found that medication, particularly in the United States, varies between northern and southern states, and between urban and rural states (Melamed-Rzhetsky, 2018).

There are many publications about the mechanisms and motivations underlying physician prescribing decisions and, in particular, about the market success of new therapies. In these publications, several micro- and meso-level factors were identified that may potentially influence the diffusion of new therapeutic options based on a literature review, which are summarized in

Table 8.

Table 8 Micro-, meso- and macro-level factors influencing the diffusion of new drugs (based on Lublóy, 2013; Keresztúri et al., 2014 and Lublóy, 2014)

Prescribing physician	**Socio-demographic factors** Gender, age, years spent in specialty, place of education, number of current jobs, nationality **Scientific orientation** Qualification, hospital working experience, participation in clinical trials, further education and clinical drug audit, number of journals read, scientific orientation, attendance at professional events, management position **Prescribing habits** Number of prescribed drugs of the same API class, number of patients or prescriptions, number of prescriptions for other drugs made by the innovator, size of the prescription's repertoire **Promotion targeted at physicians** Detailing, product samples, direct advertising to patients (DTCA) Contagion through social networking Communication with peers
Specialist consultation	**Location** (urban or rural), type (individual or group practice), size, ownership structure/management approach/profit-orientation, region, participation in training and education, diagnostic and therapeutic activities, staff structure
Patients treated	Age, health status, socioeconomic status (income, education, health insurance), marital status, ethnicity
The new medicine	**Directly measurable attributes** Manufacturer's marketing expenditure, general adoption of the drug, therapeutic novelty, number of competitors, drug price **Medical characteristics** Targeting unmet clinical needs, more advantageous therapy in contrast to available options, safety, risk- and efficacy-related perceptions
Macro level	Measures, regulations in one or more countries, e.g.: government policies

From an exploration of Lubloy's analysis on 35 studies in more detail, a list of influencing factors on the diffusion of pharmaceuticals is provided in Annex 1 (see Annex 1).

Prosser et al. also point out that the adoption and prescribing of a new drug for use is not simply based on critical biomedical assessments. There is a strong emphasis on exposure to pharmacological information about the drug and reports obtained through social contacts on the basis of which prescribing decisions are made. It is suggested that this may be the reason why differences are detected in prescribing therapeutically equivalent drugs. As a consequence of this finding, evidence-based medicine also requires a multifaceted approach (Prosser et al., 2003).

2.6.3. Personal experience of physicians (studies, conferences, practical experience)

Gallan et al. confirm the importance of physicians' experience in their prescribing behaviour. In their view, physicians' experience can be divided into two types: one concerns knowledge obtained through undergraduate education, residency training, and occasional fellowships, and the other involves personal experience with and feedback from patients about the use of medication. Decisions are made by weighing up the outcomes and side effects. Factors that correlate with 'prescribing appropriateness' include reliance on journal articles for information about new drugs, additional training, professional consultation, and a few years of experience. According to Gallan, the modern and cosmopolitan physician cares more about quality and is less influenced by sales representatives (Gallan, 2004).

While ground-breaking literature articles can play a role and motivate physicians to change their prescribing habits, the amount of medical literature that is accessible can be daunting. This may be why pharmaceutical companies strive to make their products known to physicians (Gallan, 2004).

Although in most cases physicians may prescribe drugs out of habit (Denig et al., 2002), physicians' knowledge and active consideration of available information also play an important role.

According to a study by Schumock, hospital-based continuing education plays a minor role (Schumock et al., 2004). In contrast, Anderson et al. – from interviews with US gynaecologists about their drug-prescription habits—found that prescription habits are most frequently underpinned by information obtained from further training, professional journals, and peers (Anderson et al., 2009).

Studying the changing habits associated with prescribing inappropriate antibiotics, Sbarbaro describes how collaborative workshops facilitate behaviour change, as opposed to physicians being informed only by lectures and guidelines (Sbarbaro, 2001).

2.6.4. Peers, professionals

Medical decision making is influenced by the opinions of peers. According to Campo et al., medical decision-making is most strongly influenced by formal and informal interaction with other physicians, such as in group practice, hospital settings, or medical

conferences, and by other healthcare workers (e.g., nurses) who can provide feedback on treatment outcomes (Campo et al., 2005).

Laat et al. also reinforce the role of peers in physicians' choice of medication. Interaction can take place through conferences and symposia. In these meetings, specialists can learn about new therapies and drugs. They can discuss their questions and have them answered. Furthermore, therapeutic decisions can be influenced by peers in situations when a patient contacts a specialist and asks them to re-prescribe a therapy that was started by another specialist. In this case, the previous professional's choice may serve as indirect advice to the present physician (Laat et al., 2002).

According to Scherer's study, switching between different drugs is made more difficult by established prescribing habits and potentially negative consequences for physicians of changing a prescription (i.e., the negative professional and potentially legal consequences of prescribing a new drug). However, this effect can be reduced if there is truly relevant and objective information available about competing products, and if this information is supported by peer review. In such cases, the switchover is faster (Scherer-Ross, 1990).

In a study (Svensson et al., 2019), Svensson et al. identified similar trends—namely, that Swedish GPs are more likely to start prescribing psychotropic drugs than to stop medication, and some reluctance to change other physicians' prescriptions was also revealed. In other words, when a patient is transferred to a new physician, the new physician finds it more difficult to modify the previous therapy.

2.6.5. Patient-physician interaction

In an ideal situation, the physician attempts to choose a therapy that offers the best expected outcome considering the patient's preferences. Obviously, in real-life situations such an ideal decision is not necessarily compatible with the conditions. On the one hand, neither physicians nor patients cannot be fully informed. For this reason, the expected risk-benefit ratio is not always clear even to physicians, while on the patient side only a minority of patients have the clinical and pharmacological background to understand and evaluate the appropriateness of a particular therapeutic process.

The challenge physicians face is understanding and correctly interpreting patients' complaints. It is essential that the necessary information about a diagnosis is uncovered. The social situation of patients may also influence the prescribing decision (Kee et al., 2018, Ong et al., 1995). Non-verbal communication (eye contact and careful choice of

facial expressions) is essential for effective patient-physician communication, and active listening is also mentioned as part of verbal communication. The challenge physicians face is to understand and correctly interpret patients' complaints. In a good patient-physician communication situation patients have the opportunity to share their problems, and essential, diagnosis-relevant information is revealed to the physician. As a consequence, physicians can better understand the patient's needs, so they will be able to treat symptoms more effectively (Kee et al., 2018, Ong et al., 1995).

Physicians' interaction style largely depends on patients' communication and the social situation. A comprehensive analysis by Willems et. al suggests, for example, that physicians' communication with patients from higher social classes is more active and information-rich, whereas physicians are less cooperative, more direct, and involves less information sharing with patients from lower social classes who are often disadvantaged (Willems et al., 2005).

Evidence from the literature indicates that the demographic characteristics of physicians and patients also affect prescribing decisions. These factors may include age, gender, patients' working conditions, and whether the prescriber is a specialist or a GP (Vrijens et al., 2012).

It is necessary to consider the fact that there are specific therapeutic classes related to which patient needs may be of paramount importance. Schwartz et al., in a study about cerebral and peripheral vasodilators, antibiotics, and analgesics, described how patients' requests (46%) are the most important factor in drug prescription, and prescribing to create a placebo effect—known to the physician—comes second. In this study, the recommendation of a particular treatment based on clinical experience was only the third factor (Schwartz et al., 1989). It is therefore important to consider the nature of the therapeutic class we are examining when considering the relevance of patients' requests.

According to Campo's interviews, interviewees reported why physicians do not like patients interfering with their prescribing decisions. The reason for this is the complexity of the choice environment, with decisions being left to experts. Few patients have the clinical knowledge to make the right decisions. Due to these concerns, only in exceptional and temporary cases do physicians prescribe another drug at the request of a patient. Exceptions to this are requests related to the make or type of packaging, but not to the brand. Such requests are more easily fulfilled than those for an alternative brand. Additional exceptions include when declining the request would risk the patient-

physician relationship. In such cases, for commercial reasons, brand B may be prescribed instead of brand A, accepting the patient's request, but only if brand B is still medically acceptable.

Even under high levels of decision uncertainty, physicians need to keep events under control, thus they strive to acquire information predominantly through an active, rather than a passive learning process. There is seemingly a strong need to obtain direct experience, positive or negative, of a drug before making a final decision about product choice, whatever the statistics say. It has also been shown that physicians' 'drug memory' changes slowly, because if they have been using one brand on a daily basis with their patients, they find it difficult to switch to another brand (Campo et al., 2005).

Special attention should be paid to vulnerable groups of people. While diseases are one of the causes of vulnerability, specific socioeconomic circumstances (such as the lack of a regular income, unemployment, below-subsistence income, or the need to support several dependants) can also make people vulnerable. The framework of a coverage policy can provide special protection for vulnerable groups of people (Thomson et al., 2017).

On the one hand, it seems that patients (Drozdowska-Hermanowski, 2016) are responsive to physicians' recommendations, but on the other hand, direct relationship between pharmacists and patients (Zerbini et al., 2017) seems to play a more important role.

In most countries, different stakeholders are involved in shaping pharmaceutical benefit schemes, yet patient groups are rarely represented. The consultation and involvement of patients is considered desirable based on results achieved in countries with experience in this field. If patients are involved, they understand the rationale of policy makers and can help in public debates when sensitive decisions are to be communicated to the public (such as a lack of reimbursement for medicines with limited added therapeutic benefits). Encouraging patient involvement is therefore a priority, both from the perspective of regulatory and decision-making processes (WHO, 2018).

2.6.6. Influence of pharmaceutical marketing efforts

Considering the impact of detailing on prescribing, no consistent answer is given in the literature. Some authors suggest a positive relationship between detailing and drug prescription frequency (Gönül et al., 2001), and that detailing leads to a higher return on investment. Vicciardo (1995) found from a survey of 18,400 physicians that more than

60% of the respondents started prescribing or increased their prescription of the advertised product as a result of the visit of a pharmaceutical representative (Vicciardo, 1995). According to Lieb's questionnaire, 42% of physicians expect to find a positive, influential relationship between detailing and drug prescription. The number of prescriptions was demonstrably higher when detailing was frequent compared to less frequent (Lieb-Scheurich, 2014). The actual efficiency of drug detailing is also indicated by the fact that sixty percent of physicians start prescribing or increase the number of prescriptions of the recommended product due to marketing communication activities (Gallan, 2004). Orlowski and Wateska demonstrated positive impact of symposia on physicians' willingness to prescribe certain drugs. An interesting aspect of this research is that participating physicians thought that conferences did not affect them (Orlowski-Wateska, 1992). Other authors attributed a moderate influence to pharmaceutical interactions on prescriptions (Schumock et al., 2004; Nutescu et al., 2005). There are authors who think that only a weak relationship can be found regarding this context: Mizik and Jacobsen carried out econometric analyses (74,000 doctors, over two million observations) to investigate how prescribing is influenced by sales representatives' activities. Unsurprisingly, given the large sample size, the results were significant, but the size of the effect was marginal, therefore, the effect of sales activities aiming at significant influence can be questioned (Mizik-Jaobsen, 2004). A study by Narayanan and co-authors found that marketing activities do not have a strong effect on the sales of a certain drug class, but in the long run the share of the brand is strengthened, and revenue increased. Regarding studies carried out in the US, it is important to note that the impact of direct-to-consumer marketing was also investigated, the role of which is not relevant in the European market since regulation is different. Narayanan and other authors report that detailing has a demonstrably positive impact from the perspective of marketing expenditure, while the same cannot be said about direct-to-consumer advertising (Narayanan et al., 2004). We also find literature that claims that there is no relationship between marketing efforts and drug prescription (Rosenthal et al., 2003).

In Anderson's survey, about 40% of physicians said that they first heard about a new drug from a pharmaceutical company, and only one-third of them said that they either never or rarely relied on information from sales representatives, and this was particularly true for physicians working in the private sector (Anderson et al., 2009). Groves et al. concluded that drug samples are very useful when introducing a new product to market, competing with another drug, changing the image of an existing product, or boosting demand. Their study concludes that drug samples are critical in the introduction and promotion of new

products (Groves et al., 2003). Sorescu and his colleagues pointed out, that with the help of powerful marketing activities, large-volume innovations can be turned into significant financial results (Sorescu et al., 2003). In a study, Dolovich observed antibiotic prescriptions in an active group of 641 (influenced by sales representatives) and a control group of 574. There was no noticeable difference between the two groups when examined as a whole, but it was found that female physicians were slightly more willing to give in to the influence of sales representatives than male physicians, and that recent graduates were more likely to prescribe new drugs (Dolovich et al., 1999).

Leeflang et al. attribute their controversial results to the inaccuracy of the research. The related study revealed that the research did not examine marketing expenditure on brand portfolios consistently, which may result in bias, and physicians' receptivity is not necessarily the same in relation to various forms of therapy promotion (Leeflang-Wieringa., 2010). Studies that used aggregate data for analysis concluded that manufacturers' marketing efforts (i.e., detailing and symposia) have a positive impact on drug sales, and while the effect is indirect for 6–14 months after the product launch, thereafter pharmaceutical marketing communication, of which drug detailing is an integral part, has a direct effect (Chintagunta-Desiraju, 2005; Narayanan et al., 2004; Narayanan et al., 2005; Neslin, 2001; Rizzo, 1999). The previous examples illustrate that the statement, although validated at the aggregate level, may not be universally applicable to each therapeutic class and in every case. Therefore, it is essential to examine the issue in detail.

Following on from the foregoing, Venkataraman and Stremersch—similarly to Azoulay—examined the interplay between scientific appropriateness and prescriptions (indirect sales) in detail (Venkataraman-Stremersch, 2007). The study investigates, for the US pharmaceutical market, how the marketing activities of industry players (detailing and professional symposia, as well as B2C activities reflected in patients' requests) influence the impact on drug prescription if the drug is clinically preferable (in terms of safety and efficacy), and if it is not, why not. In the econometric model, authors studied the following factors:

- Two-year detailing of a US pharmaceutical company in detail, broken down by month, for three classes of drugs (statins, gastrointestinal agents, erectile dysfunction).
- Attendance at symposia organized by the manufacturer for physicians.

- Drug requests of patients from the studied 2,774 physicians.
- Number of prescriptions and quantity of drugs dispensed.
- Efficacy (meta-analysis of clinical trials, ‘Z-scores’ compared to placebo).
- Side-effect profile (FDA, drug approval database)

The theory suggests that more effective therapies can reduce physicians’ uncertainty, making it easier to convince them of the benefits of these drugs through various marketing efforts (as described in Azoulay’s work in 2002). Regarding safety, drugs with a riskier side-effect profile evoke feelings of uncertainty in physicians. This feeling of uncertainty can be diminished by marketing activity, although physicians give priority to safer therapies for the reasons described above. Among the findings, it is important to underline that different classes and brands of drugs should be considered individually, otherwise it would be difficult to make general statements. Nevertheless, it is confirmed that prescribing rates are higher when more effective or safer therapies are being investigated, and in these cases physicians are more responsive to patients' expectations as well.

Physicians may have less information about specific drug therapies than pharmaceutical manufacturers. From this point of view, pharmaceutical marketing activities can help physicians and thus improve the effectiveness of their work. Additionally, marketing can also persuade physicians to use a product for a wider range of indications (Laat et al., 2002).

Marketing activities can transform decisions into routine decisions. In Campo's research, physicians talked about their routines whereby they had previously used drug A or B in 80% of cases, and after learning of a new drug or drugs sometimes switched to prescribing them as an experiment. Then, if the new drugs produced positive results, they could substitute drugs A and B (Campo et al., 2005). However, there is also evidence that pharmaceutical manufacturers’ efforts and marketing activities are more harmful than helpful. Gallan, from a survey of patients, found that the majority of those surveyed believed that the pharmaceutical industry had been a little aggressive or too aggressive in their marketing. Despite this, two-thirds of the respondents trusted their physicians to make the right decisions and only eight per cent said it would have been better if their physician had not met with sales representatives (Gallan, 2004).

The impact of pharmaceutical marketing on prescribing costs can be both negative and positive. Caudill et al. demonstrated that the more intense the detailing and higher the

credibility, the higher the prescribing costs, a correlation that is particularly pronounced for physicians who practice in non-academic settings (Caudill et al., 1996). However, marketing can also have the opposite effect on price, as Leffler pointed out: advertising has a positive effect on price competition (drug prices go down) through its two functions of providing information and exerting influence (Leffler, 1981). Steele compared three groups: in the first group, clinical pharmacists visited physicians; in the second one, written evaluation physicians' prescribing habits were compared with those of others; and the third one involved a control group with no intervention. After the intervention, changes in the number and cost of prescriptions were investigated. The number of prescriptions did not change in either group, but the first group was associated with a significant reduction in prescribing-related costs (Steele et al., 1989).

2.6.7. The role of price in drug prescription

The role of price in the decision-making process can vary widely across countries, thus the literature is not consistent regarding whether marketing expenditure can reduce price sensitivity. Ceteris paribus, physicians should choose the cheapest therapy, which may be strongly modified by the persuasive function of marketing, especially since the ceteris paribus principle is very difficult to evaluate among drug therapies (De Laat et al., 2002; Leffler, 1981; Hurwitz-Caves, 1988). If as a result of companies' marketing activities physicians become less price sensitive, then this process, as interpreted by De Laat et al., leads to an 'increase in brand loyalty based on non-product attributes' (De Laat et al., 2002, p. 80). This results in higher prices, which ultimately results in social losses (Windmeijer et al., 2006). In contrast to Windmeijer et al, Leeflang and Wieringa argue that this effect is not typical (Leeflang-Wieringa, 2010). Regarding their study, it is necessary to mention that it was carried out in the quasi fully financed pharmaceutical market in the Netherlands. This example illustrates that there may exist financing systems in relation to which physicians and patients do not need to consider the role of price.

In a study of hospital-based small molecule heparins, physicians ranked the role of price behind efficacy, safety, guidelines, and personal experience, but ahead of factors related to the influence exerted by the pharmaceutical industry and peers (Nutescu et al., 2005). Despite this, physicians are often unaware of or wrongly perceive the price of drugs, and information campaigns organized for them about prices encourage the prescribing of cheaper drugs (Hart et al., 1997; Allan et al., 2007; Polinski et al., 2008).

Manchanda et al. suggest that the existence of health insurance and increased reimbursement can reduce the price sensitivity in the pharmaceutical market. This statement explains why authors who investigate different countries may have very different results (Manchanda et al., 2005). It is therefore essential to compare the pharmaceutical policy instruments of the countries under consideration.

It is crucially important to prioritize, as due to budget constraints public financiers cannot subsidize all drugs and drug prices in full. Policy makers face difficult choices and need to make compromises in relation to national priorities. Transparency in the priority-setting process is important, and the disclosure of the potential interests of consulted and affected parties should be enforced (WHO, 2018).

Price control of drugs is another key element of the pharmaceutical policy framework that ensures protection for health insurance funds. Price controls help to reduce prices: the introduction of them has been a major step forward, particularly when patients had to pay for many drugs entirely out of pocket. The WHO study shows that in most European countries the price of reimbursable drugs has been regulated. Accordingly, price regulation supports public funders to limit their costs and thus offer a wider range of services (more reimbursable drugs) and/or smaller deductibles (WHO, 2018). In turn, a lower price can make a drug more attractive to physicians/patients, thus increasing prescription frequency. If pharmacists are qualified to select the API-containing drugs prescribed by the physician, cheaper drugs may be preferred according to national regulations. Further, financiers may give preference (through reimbursement) to particular products on the basis of cost-effectiveness.

2.6.8. Pharmaceutical policy / reimbursement policy

Ensuring access to essential drugs can significantly contribute to improving public health. In countries where access is not guaranteed, or where the share of out-of-pocket financing is large, patients may forgo or postpone prescribing or buying drugs, or may be unable to obtain access to care for financial reasons (Goldman et al., 2007; Niëns et al., 2010). This may lead to the more rapid spread of disease or poorer health status. The same trend was confirmed by a WHO study (WHO, 2018)—namely, the abolishment or decrease of deductibles had a positive effect on medication adherence and helped to achieve better health outcomes. Furthermore, the introduction of or increase in co-payments has resulted in a decrease in the number of per-capita prescriptions, a reduction in public drug expenditure, greater financial burden on patients, and a reduction in medication adherence

(WHO, 2018). Liao et al. showed (Liao et al., 2020) that the prescription volume of innovative oncology drugs changes dynamically as they are included on the list of reimbursed products, and both endogenous factors (changing national reimbursement conditions) and exogenous factors (competition) influence the volume of prescription products.

Public investments in pharmaceutical expenditure—which involve careful consideration of the three components of general health insurance (coverage of the population, range of available services, and extent of financial protection against the costs of healthcare services)—contribute to the development of a fair reimbursement policy framework, while inefficiencies in the health system and inadequate attention to the needs of certain vulnerable populations can undermine such efforts. Therefore, increased investment will not automatically lead to affordable access to drugs for everybody if some components of Universal Health Coverage (UHC) are not prioritized (WHO, 2018).

Pharmaceutical policy can influence drug choice not only through reimbursements but also by delegating drug choice decisions. Danzon and Furukawa proposed a distinction between two types of markets: physician-driven markets, where physicians decide which manufacturer's product to prescribe, and pharmacy-driven markets, where it is essentially the task of pharmacies to decide which company's product containing a particular active ingredient to promote/market (Danzon-Furukawa, 2011). In a study by the latter authors, the US and the UK were designated as being in the latter category, while physicians' prescribing decisions were found to be the dominant factor in Italy, Germany, Spain, and France. Partly as a result of pharmaceutical policy measures that were introduced in the wake of the economic crisis of the late 2000s, this boundary seemed to blur in several countries, but at least the role of pharmacies was strengthened (Leopold et al., 2014). In the EU, mandatory drug prescription or mandatory generic substitution has already been introduced in the legislation of ten countries, and is encouraged in some way in most countries (Vogler et al., 2017a). This increasingly strengthens the role of pharmacies in determining which product is ultimately delivered to patients, but the decisive role in terms of the choice of API remains with the physician.

On the demand side of the pharmaceutical market, prescribers and other professionals are also the targets of measures aimed at limiting costs or increasing efficiency through quality assurance (see Table 9). Such measures need to balance the scientific independence and professional expertise of prescribers together with the overall optimization of drug supply. In most European countries, physicians have the exclusive

right to prescribe drugs and thus play a crucial role in the reasonable use of drugs (Panteli et al., 2016).

Another strategy for strengthening sensible pharmacotherapy and improving efficacy is developing prescribing guidelines. These are formulated by financiers, national health authorities, or professional associations, and are more or less binding in their implementation. In most countries they are seen as guiding principles for high quality, efficient care that do not override the professional judgement of prescribers. The same applies to the monitoring of prescribing behaviour and volumes (Panteli et al., 2016).

Table 9 Measures for improving quality and efficacy (Panteli et al., 2016)

Country	**Pharmaceutical budget**	**Prescribing guidelines**	**Incentives, sanctions**	**Electronic prescribing**	**Prescription monitoring**
EK – England	Yes (NHS –> CCGs –> GPs)	Optional	Incentives	Yes	Yes
EK – Scotland	None	Optional	None	Yes	Yes
FR	None	Optional	As part of performance payment ("*Rémunération sur Objectifs de Santé Publique*")	Yes (subscription possible)	Yes
NL	None	Optional	None	Yes	Yes
PL	None	Optional	Penalties for incorrect prescriptions	Yes	Yes
DE	None	Mandatory	Exceeding target quantity may require recovery	Yes	Yes
IT	Yes (for GPs, regional and local health authorities)	Optional	Incentives (regional); sanctions are theoretically possible, not enforced	Yes (partially introduced)	Yes (regional and local health authorities)
ES	None	Optional	Incentives	Yes	No

In a study of 2189 inpatients, Wang et al. (Wang et al., 2018) found that the essential drug cost ratio was higher with older physicians and with those who scored higher on the NEMS (National Essential Medicine System of China). Physicians with higher academic qualifications and more work experience tended to prescribe fewer essential drugs. The prescribing costs of essential drugs were proportionally much higher for physicians without a professional title than for those with a senior title. Physicians who were employed through recruitment agencies prescribed fewer essential drugs than contract physicians.

2.6.9. Impact of reimbursement policy

Recent publications have examined the impact of five interventions/changes in reimbursement policies. The five areas under investigation were the impact of increasing deductibles, eliminating co-payment, introducing co-payment policy, introducing general guidelines, and slimming down the reimbursement system. In the following, I summarize research findings about each of these measures.

2.6.9.1. Increasing deductibles

Research by Fiorio and Siciliani (Fiorio-Siciliani, 2010) carried out in Italy revealed that as the out-of-pocket expenses of patients increase, the number of per-capita prescriptions decreases and, of course, per-capita public expenditure on pharmaceuticals also decreases. The results of research by Sinnott et al. (Sinnott et al., 2016) undertaken in Ireland showed that adherence to essential and less essential drugs decreased. Further, Puig-Junoy et al. (Puig-Junoy et al., 2014; Puig-Junoy et al., 2016), confirming the findings of Fiorio CV and Siciliani L., found in their research in Spain that the number of prescriptions and drug consumption (in DDD) and public health expenditure also declined.

2.6.9.2. Elimination of co-payment

Elhayany and Vinker (Elhayany-Vinker, 2011) found for Israel that there was an improvement in adherence to medical advice among residents with chronic illnesses who were less economically well off. Atella et al. (Atella et al., 2006) were able to demonstrate a potentially positive effect of co-payment discontinuation on health and medication in an Italian sample.

2.6.9.3. Introduction of co-payment policy

A study by Daminai et al. (Daminai et al., 2013; Daminai et al., 2014) showed an increasing trend to the use of statins and a negligible decrease in the use of selective serotonin reuptake inhibitors in Italy. Ong et al. (Ong et al., 2003) found no effect on drug use in Sweden, except for a decrease in the use of antidepressants. Gemmill et al. (Gemmill et al., 2008) and Luiza et al. (Luiza et al., 2015), who based on their research on several European countries, found an inverse association with drug use—i.e., a decline in drug use and a decline in drug expenditure.

2.6.9.4. Impact of generic drug prescription policies on prescription (internal reference prices and generic substitutes)

Koskinen et al. (Koskinen et al., 2014), based on research in Finland, revealed that measures led to a reduction in the daily costs of antipsychotic drugs for the financier. Andersson et al. (Andersson et al., 2006) and Granlund—both groups of authors working from a Swedish sample—also identified a decline in the expenditure and volume of all drugs (Granlund, 2010), Granlund also demonstrated a reduction in average drug prices. Research by Moreno-Torres et al. (Moreno-Torres et al., 2011) on a Spanish sample and research by Barros and Nunes (Barros-Nunes, 2010) on a Portuguese sample suggests that the medium- or long-term control of expenditure is ineffective. Vogler et al. (in Denmark) were able to show a positive effect on the affordability of drugs; i.e., a policy on appropriate generics made preparations more affordable (Vogler et al., 2017b). The results of research in Austria by Gouya et al. indicate that with an increase in the share of generic drug expenditure within total expenditure, more generic drugs are prescribed, and expenditure per prescription decreases (Gouya et al., 2008).

2.6.9.5. Limitations of the reimbursement system

Based on the research results of Hoebert et al. conducted in the Netherlands, the number of prescriptions and the extent of their use are decreasing, while Damiani et al. (Damiani et al., 2014) experienced an immediate decrease in the trend to and level of statin use in Italy (Hoebert et al., 2012).

2.6.10. Factors influencing generic drug prescription

Attitudes towards generic drug purchase may be influenced by perceived quality, product attributes, previous experience, and physician recommendations (Ferreira et al., 2017). Product attributes can affect attitudes and purchase intentions. In this context, a literature review revealed that understanding attitudes and purchase intentions during consumers' journey in relation to purchasing generic drugs has been a challenge (Madahi-Sukati, 2012).

Arcaro et al. (Arcaro et al., 2021) identified three main factors associated with consumer attitudes and purchase intentions for generic medicines: consumer attitudes and behaviour; patients' and health professionals' views; and risks associated with generic drug use.

Among the most important factors affecting generic prescription, I will describe the following ones based on the literature:

- Price, cost
- Beliefs about risks and efficacy, confidence
- Patients' attitudes
- Other factors (legislation, socio-demographic characteristics)

In general, authors have focused on more than one factor in their research, in which case I present the results of the most important factor in the relevant subsection.

2.6.10.1. Price, cost

In several studies authors conclude that the price-reducing effect of generics is an undeniable benefit, especially in countries with lower health insurance penetration.

A WHO study supports the use of generic, biosimilar, and other lower-priced drugs. Lower-priced drugs, such as generic drugs, offer an excellent opportunity to make drugs available at a lower cost. This means lower costs for patients and opportunities for making cost savings for public financiers. Evidence from the literature and the analysis for this study indicates the importance of strengthening confidence in the quality of generic drugs and the relevance of demand-side measures to facilitate the diffusion of generic drugs and other lower-priced drugs (WHO, 2018).

Olsson and Kalvemark Sporrong (2012) interviewed Swedish pharmacists and found that most of them support generic substitution due to economic benefits, but they also lack information about them. The efficacy of generics is considered adequate; the same as that of the original products (Olsson-Kalvemark Sporrong 2012).

The impact of price can be felt not only at a micro- but also at a macroeconomic level, as illustrated by a WHO (2018) study which reported that introduction of RPS and generic substitution has reduced public drug expenditure in the studied drug classes through a reduction in drug prices. Pricing policies that complement reimbursement models, such as RPS and generic substitution, have also had a positive impact on creating more affordable drugs and increased the use of generic drugs (WHO, 2018).

Purchasing attitudes and purchasing intentions are sensitive to economic recessions, and when product prices, including drug prices, go up (even if not in absolute terms, but in relative terms), people turn their attention to cheaper products. From the perspective of consumers, the perceived risk associated with the use of generic drugs decreased in Brazil during the economic crisis (Ferreira et al., 2017).

However, there are examples of the opposite trend as well. From a survey, Tsiantou et al. (2009) found that 75 per cent of Greek physicians were not affected by pharmaceutical manufacturers' sales representatives and, although more than half of the respondents rated drug prices as high or very high, they said that sales of generic equivalents under the INN name should be authorized (Tsiantou et al., 2009). Theodorou et al. (2009) also conducted research in Cyprus and compared physicians in the two countries and found that while only 25% of Greeks prescribe generic products, 66% of Cypriots do so. It is a very important determinant whether patients have to pay for the drug from their own pockets (60% indicated this was 'important' or 'very important') (Theodorou et al., 2009). In other words, the legal framework and the financing system also affect the choice of drugs.

2.6.10.2. Beliefs about risks and efficacy, confidence

Nardi and Ferraz interviewed 150 opinion leaders and patients to investigate the perceptions of consumers, physicians, and pharmacists about generic drugs. Their findings suggest that several factors can influence the purchase of generic drugs. They also demonstrated that price is an important factor, and that efficacy, safety and trust are also significant determinants of drug choice (Nardi-Ferraz, 2016).

Ferreira and Barbosa investigated attitudes towards the substitution of innovative medicines with generics by interviewing 218 patients. Based on the results, participatory decision-making has no effect on the intention to purchase generic drugs, while perceived risk and price awareness have a significant effect (Ferreira-Barbosa, 2017).

Saposnik et al. in their study—involving an analysis of individual responses from neurologists using linear regression models on a database of 117 questionnaires—pointed out that more prescriptions for generic drugs are associated with higher TI scores. (Therapy Inertia was defined as the lack of initiation or escalation of treatment in cases when evidence of clinical and radiological activity was available [Saposnik et al., 2018]).

Risks associated with generic drugs were demonstrated in the study of Heikkilä et al. on generic drug substitution (Heikkilä et al., 2007). When consumers consider making a generic substitution of a reference drug, they usually weigh the risks against the benefits (cost savings) and base their decision on these factors.

In the USA, Shrank et al. revealed more uncertainty in their study: roughly a quarter of physicians (23%) commented negatively on the efficacy of generic drugs, and almost 50% also evaluated their quality negatively (Shrank et al. 2011). This trend was

particularly noticeable (three times more frequent) among older physicians. Research by Fabiano et al. (2012) carried out in Italy showed that although the majority of physicians consider generic drugs to be effective, only 14 percent of them said that at least half of their patients were treated with generic drugs. This low rate is mainly due to scepticism about the drugs (Fabiano et al. 2012).

As to the risks associated with physicians and patients using generic drugs, Straka et al. highlight that three important factors need to be considered: patient attitude and adherence, potential divergence in clinical outcomes, and extent of cost and resource use. In their comprehensive study they underline that all three types of risk need to be considered simultaneously for a successful generic switch, otherwise the cost reduction target may not be met (Straka et al., 2017). Clinical efficacy was reported by 71.9% of physicians in Saudi Arabia as the most influential factor affecting prescription of originator products over generic drugs (Salhia et al., 2015).

Gómez and Rozano (Gómez-Rozano, 2012) used a questionnaire survey based on interviews with 542 physicians, pharmacists, and patients to study causal relationships that influence consumer purchase intention, including perceived risk, experience, and prior information provided by physicians and pharmacists. They found that the higher the perceived risk, the lower the motivation to ask for generic drugs, this effect being reduced by the positive effect of experience.

Dunne and Dunne systematically reviewed 58 published studies with a focus on physician, pharmacist, and patient perspectives. They found that a key factor in improving the confidence of these groups is information and education, particularly about equivalence, regulation, and dispelling myths about generic medicines. Improving the perception of generic drugs within physician groups may be critical to improving use and adoption of generic drugs in the future (Dunne-Dunne, 2015).

A study conducted in Slovenia (Kersnik-Peklar, 2006) showed that 90 percent of physicians felt that generic drugs were as effective as their original counterparts. Furthermore, one in four increased their prescription of generic drugs if their effectiveness was adequately validated by clinical trials.

Arcaro et al.—from an analysis of 13 studies on attitudes towards generic drug purchase—concluded that factors related to attitudes and purchase intentions can provide insights that may guide promotional strategies for the use of such products. Arcaro et al.

came to a parallel conclusion in a WHO study (WHO, 2018): positive perceptions should be generated among physicians, health professionals, and patients (Arcaro et al., 2021).

2.6.10.3. Patients' attitudes

Muzumdar et al., from a survey of 2222 consumers, investigated how the consumer intentions of generic drug users are shaped using the theoretical framework of planned behaviour theory. Attitudes, subjective norms, and past behavior have a positive effect on generic drug purchase intentions, but no effect on perceived behavioral control. Risks, trust in pharmacists, brand sensitivity, and self-identity can influence generic drug purchase (Muzumdar et al., 2013).

Gill et al., after interviewing 15 pharmacists in Finland, Australia, and Italy, found that pharmacists in all three countries perceived it as a professional challenge to inform patients about generic substitution. Several reported that patients did not believe in the efficacy of generic drugs (Gill et al., 2010). This is a good example of how the introduction of generics can also encounter obstacles in relation to patients. From the current research about the topic, five insights have been identified that can provide a strategic direction for companies that market generic medicines. It is suggested that a more positive perception of generic drugs needs to be generated to enhance purchase intentions and reduce barriers between different healthcare systems in order to implement policies and promote industrialization, commercialization, and access to generic drugs.

In summary, the evolution of consumer attitudes towards generic drugs can be divided into two periods: Before 2013, and after 2013. Publications from before 2013 basically focused on decision-making and risks. After 2013, products were the focus of decision-making studies and were viewed through different lenses: cost-benefit analysis (Ferreira et al., 2017; Tian-Zhou, 2015), marketing communication (Newman et al., 2016), public policies (Zerbini et al., 2017), and the quality of generic drugs (Kauppinen-Räisänen et al., 2012). Similarly, risks can be classified into those associated with drugs, generic substitution, and patient attitudes, which may suggest that patients are sceptical about the efficacy of generic drugs, reinforcing the need to improve communication with health professionals and end consumers (Dunne-Dunne, 2015), as well as to facilitate access to generic drugs (Prashanth et al., 2016).

2.6.10.4. Other factors (legislation, socio-demographic characteristics)

Skinstad conducted a study in Norway, where legislation requires physicians to use generic substitution unless the physician rules it out, or the patient refuses this and is ready to pay the price difference. Seventy-five per cent of the physicians who were interviewed have a positive attitude towards the system and only complained about its time-consuming nature. However, it should be emphasized that the main reason why physicians had prescribed the original preparation was because they remembered the brand name only, and they also trusted that the pharmacist would find a substitute for the drug (Skinstad, 2012).

Figueiras et al. surveyed 1278 patients to investigate, among other things, the impact of sociodemographic factors on the purchase of generic medicines. They found that beliefs about the use of generic drugs were related to the age and education level of the respondent: older people were less likely to favour such products than younger people; similarly, the higher the level of education, the more receptive people were to generics (Figueiras et al., 2008).

Tuncay et al. revealed that GPs have an increasing tendency to describe generic drugs; there is little gender difference in terms of prescribing Rx drugs, with female GPs slightly more inclined to prescribe fewer generic drugs than male GPs; and finally, in terms of diagnoses, generic drug prescriptions are concentrated in a specific area, related mainly to diseases of the circulatory and digestive systems. The prescription of generic drugs also depends on the different diagnoses, and additionally, when the number of prescribed drugs and/or the number of off-patent APIs is large, the market offer of generic drugs is also high (Tuncay et al., 2020).

The adoption of generics is clearly supported by several studies. A study by Paraponaris et al. revealed that three-quarters of French physicians are willing to prescribe generic drugs regardless of their gender, age, length of practice, the sector in which they work, and the economic situation of the geographical area of their workplace (Paraponaris et al. 2004).

2.7. Prescribing rights of pharmacists and the impact on drug choice in Europe

In Europe, prescribing is a controversial issue because pharmacists do not have the right to prescribe medicines, but this is much more common practice on other continents (i.e., Canada, USA, Australia, and New Zealand) (Garattini-Padula, 2018).

To have prescribing authority, a physician or a pharmacist must have an appropriate professional background (including diagnostics), and be legally responsible for the consequences of their decisions. Even if all these conditions are met, it is very likely that expanding pharmacists' prescribing rights would create tension between the pharmacists and physicians traditionally responsible for prescribing (Garattini-Padula, 2018). In terms of prescribing rights, it is necessary to distinguish between institutional and community pharmacists. Garattini et al. (2021) report a partial increase in pharmacists' prescribing rights and point to the increasingly important role of hospital pharmacists in recent years (Garattini et al., 2021). This role is being enhanced by their specialization in specific therapeutic areas (i.e., dermatology, neurology, or oncology) and by their multidisciplinary approach to strengthening their independent opinion, thus increasing the prescription of cost-effective—generic—medicines in hospitals. This gives them a say in what medication is recommended by specialists. Third, hospital pharmacists have extended their knowledge to medical devices. Another important area to be developed is the practice of private pharmacies, since in their case it is crucial to build a well-functioning commission system, as commissions calculated as a percentage of drug prices (e.g., France, Spain, Italy) do not encourage the choice of cost-effective generic preparations but rather the prescribing of original, expensive drugs.

Community pharmacists in Europe are among the most accessible and visible health professionals in primary healthcare. Most of them still work in small or medium-sized pharmacies, where a (high) return on investment is needed. This type of profit-oriented retail approach may conflict with ensuring optimal health outcomes at the societal level. In order to achieve cost savings from lower-price generics at a societal level, the widespread diffusion of generics is needed. This in turn requires the involvement of those responsible for drug selection, including pharmacists. When patients buy prescription drugs, pharmacists have the option of providing a generic product, subject to the possibilities defined by the legislation. Whether pharmacists choose a generic product or not largely depends on the nature of the remuneration they receive. There are several ways in which pharmacists' remuneration can be determined (Dylst et al., 2012):

- it can be defined as a percentage of the price of the drug—this clearly penalizes prescribing generic products,
- using a guaranteed margin—the pharmacist's commission is the same both on originators and generic products,
- performance-based payment—the basis for calculating commission is the volume that is soldm not the price of the medicine

In Europe, these trends are only observed in a few countries, and only to a limited extent (Garattini et al, 2021):

- The United Kingdom was the first country where pharmacists were granted prescribing rights (supplementary prescribing) in 2003, subject to completion of a specific prescribing course and registration with the relevant regulatory body. The supplementary prescribing model has become subject to prior diagnosis and an agreed and signed clinical treatment plan, developed in collaboration with the patient's GP or hospital physician (the independent prescriber), the prescribing pharmacist, the prescribing physician, and the patient. Once this plan is in place, clinical responsibility and prescribing can be delegated by the physician to the supplementary prescriber.
- In Germany, for example, all ACE inhibitors are considered ‘au idem’, so unless physicians forbid it, pharmacists can override physicians’ decisions about a product and can prescribe a different API.
- Retail pharmacists in the Netherlands have the right to intervene in a prescription if it does not comply with the national guidelines or does not seem appropriate for the patient.
- In Hungary, the pharmacy generic incentive scheme was introduced in 2012, under which the rules on operating subsidies for small pharmacies and the system for claiming and paying interest-free advances were amended. The system favours pharmacies with a lower turnover, on the one hand, and promotes a higher proportion of sales on the other, and thus—within the fixed subsidy group—drugs within the price band are preferred, and in the absence of such a price band, the reference drug, or drugs with equal or lower daily costs than the reference drug, are used. The main objective of the measure was to increase the dispatch rate of

the promoted prescriptions. It is true that in the two years following its introduction the proportion of promoted prescriptions increased from 50% to 60%, but after this it started to stagnate. A further point of criticism is that subsidies were homogeneous rather than differentiated; i.e., pharmacies received subsidies irrespective of their size.

2.8. Crucial envelope theories in the research framework

During my doctoral research, the service-dominant logic (SDL) approach of Stephen Vargo and Robert Lusch was the most influential marketing theory. Conducting my research within the complex framework of the pharmaceutical industry, I fully identify with the basic theses of SDL. The paradigm-shifting work published by the authors had several antecedents. Quoting Achrol and Kotler: '...a paradigm shift in marketing has already approached the horizon' (Achrol-Kotler, 1999). Rust draws attention to the fact that the classic approach to service marketing—in which service market phenomena are integrated into models valid for physical goods—is outdated (Rust, 1998). Gumesson, as a forerunner, formulated a similar idea: 'Consumers do not buy products or services, but offers that provide value-creating services' (Gummesson, 1995).

Vargo and Lusch describe how the approach had changed from a product-based one to a customer-centered, service-based approach by the beginning of the twenty-first century. The study emphasizes that a paradigm shift has occurred in the field of marketing. The authors are the first to synthesize the new paradigm, the result of which is a strongly attitude-shaping framework. The study does not criticize the dominant marketing thinking of the past. On the contrary, it seeks to explain in a logical way why the frameworks thus described have gained legitimacy in the respective eras. It is considered clear that, from the beginning of the industrial revolution, tangible material goods and their possession were the main sources of value. Initially, marketing existed separately from production; its only role was to help goods change hands. With the accumulation of practical knowledge and the development of theories, more and more analytical procedures appeared which companies could use to search for optimal solutions. Due to intensifying competition, the focus was increasingly on satisfying the consumer and the use value of the products for the consumer. The various functions of the company became increasingly intertwined, but in addition, the individual areas were more deeply characterized by micro-specialization; i.e., actors in the process participate in increasingly specialized and

narrower sub-processes during value creation. Micro-specialisation is perhaps one of the most obvious features of the pharmaceutical industry (Vargo-Lusch 2004).

To understand the continuous evolution of thought this involved, the authors introduce the concepts of passive (operated/operand) and active (operating/operant) resources. The passive resources discussed in conventional thinking are those for which some action must be taken to achieve an effect. Active resources, on the other hand, are those that can produce an effect on their own. Passive resources are finite and can be considered static. In contrast, the finite nature of active resources is often unknown, and they dynamically change. They are also intangible and, because of their operational nature, capable of multiplying passive (and even active) resources. The human mind and organizational knowledge are very good examples of active resources. These are the resources that lead to the innovation of newer and newer drug therapies and ensure that they are delivered to patients.

Based on a synthesis of knowledge from the literature, the authors conclude that service-centred marketing consists of successive social and economic processes. These processes are organized around active resources and are aimed are creating differentiation from competitors. Continuous improvement and iteration are now default elements of the processes in value creation. The fundamentals of this approach can be summarized in four points:

1. The focus is shifting from the production of products and related logistics to the identification of competencies that can provide a potential competitive advantage.

2. In the past, products were produced completely separately from the market for reasons of efficiency. According to the new approach, the consumer is an active participant in value creation, and in order to meet specific needs the producer must pay particular attention to the individual needs of the consumer.

3. Based on the competences of the organization, it is essential to analyse who else could be a potential customer, in line with the competences that are available.

4. Conclusions must be integrated into the processes through the continuous analysis of market feedback.

Even from these four points, the main pillars of the conceptual framework stand out, but Vargo and Lusch explain the theory even better using eight premises:

1. Highly specialized skills and knowledge become the basis for exchange. At the beginning of industrial production, the basis of exchange was the product. However, authors say that this exchange is an exchange of services. In this, they take a completely different perspective on the same process.

2. Due to micro-specialization mentioned above, the basic unit of exchange is becoming increasingly unclear to those involved in the process. Due to the high level of specialization, processes are becoming increasingly fragmented and the increasing number of actors who aim to meet this demand are moving further and further away from the consumer, as is the case of the pharmaceutical industry. This process is naturally accelerated by the growth in the size of companies.

3. In spite of the classical approach, the purpose of the product in the centre is to embody the service. In this interpretation, physical products are replaced by direct services and competences (e.g. the work of an accountant is replaced by a computer program).

4. Knowledge, as an active resource, becomes the most decisive element of competitive advantage. Social knowledge, as understood in neoclassical terms, becomes an endogenous variable instead of an exogenous one.

5. Since there is an exchange of services in the market instead of products, it is in fact better called a service economy.

6. In the process and in the consumer-feedback-centred conception, consumers participate in the value creation process. In this interpretation, the product is only an intermediary.

7. Since the consumer is also an active participant in value creation, the company can only make an offer regarding its products; the price is not determined by them.

8. Service-oriented marketing is consumer- and relationship-oriented. This statement is fully consistent with premises six and seven.

I believe that the authors have synthesized the available knowledge in their study in a very logical way, revealing the interplay between them, and laying new foundations. In interpreting what has been written so far about the pharmaceutical industry and in relation to the field of my research, I should incorporate two additional theories into the research framework: Porter's value-based health service model, and evidence-based medicine on

the medical and pharmaceutical side. As already discussed, evidence-based medicine is meant to examine which of the available therapies is the most beneficial, based on the available, clinically reliable body of knowledge and on the safety and efficacy attributes of the drug therapy. Porter and Teisberg's theory complements this by examining health value in the numerator as a function of the cost necessary to achieve the health value in the denominator, and suggesting that health decisions should be made using the cost/benefit principle defined in this way (Porter-Teisberg, 2006). Considering the pharmaceutical industry in this framework, with the addition of Vargo and Lusch's theory, the following conclusions can be reached:

1. Pharmaceutical industry players need to view the production and distribution of pharmaceuticals as a service aimed at maintaining health or treat diseases (Vargo and Lusch).

2. Drugs with the highest therapeutic value for patients should be preferred (EBM and Porter). (This is accompanied by Porter's cost perspective, which in the case of pharmaceuticals is less decisive from the patients' and physicians' point of view, but relevant to the financier and regulator.)

3. The most important issue is identifying the competences that can create a potential competitive advantage. As prescription drugs are not objects of desire but objects of real need, my research is focused on clinical appropriateness. Clinical appropriateness (EBM) → (leads to) more beneficial, higher-value health outcomes (Porter) → improved service quality (Vargo and Lusch). Based on the competences of the organization, it is essential to analyse who else could be a potential customer. This is particularly important in relation to the complex system of pharmaceutical sales (EBM, Porter, Vargo and Lusch).

4. Consumers (physicians, patients, and indirectly, the financiers) must actively participate in the process of value creation. The decision-making process needs to be examined with this focus (Vargo and Lusch).

5. Conclusions must be integrated into the processes through a continuous analysis of market feedback. This is also an important aspect of my doctoral research in terms of practical applicability (Vargo and Lusch).

3. Methodology

3.1. Interpretation of the field of research according to the Maxwell research model

The first and most important issue is to formulate **research objectives and questions** that address economically relevant and socially important issues, without being self-absorbed, insofar as this is possible. As a scientific work, the novelty of the research results should of course not be overlooked. My research questions, as outlined in the introduction, aim to explore the following assumptions:

- To what extent does clinical evidence determine the extent of drug use? That is, are the clinically most appropriate therapies made available to patients?
- What other factors influence drug use?
- What is the interplay between the factors that influence drug use?
- Is there a country-of-origin effect in the pharmaceutical market?
- To what extent can EU pharmaceutical markets be considered similar regarding the questions above?

I used qualitative methodology in my doctoral research to clarify the interconnections and to generate theories. In the thesis I highlight the role of the product among the marketing elements, with clinical appropriateness being a key factor among product attributes. My initial assumption is that, ideally, this single factor should determine prescription and hence sales of drug therapies. During both the secondary research and the expert interviews this factor was kept in focus, and the aim of the literature review was to explore the importance of clinical appropriateness and how it is reflected in drug sales. The literature review has covered both clinical appropriateness, physicians' perceptions, and the pharmaceutical marketing mix. However, no comprehensive work can be found that provides a theoretical framework for the idea of how the impact of clinical appropriateness is communicated to the patient in relation to the complex interrelationships that exist in the pharmaceutical market, and there is no literature that provides guidance on how this can be researched coherently. This was also the focus of the expert interviews and interviewees were asked to systematically help answer the question how decision makers are influenced by more beneficial clinical attributes of a medicinal product. This question is discussed at greater length in the medical and pharmaceutical literature, but the functioning of the market is neglected by these disciplines. Throughout the entire work, I have therefore aimed to use a multidisciplinary

approach wherein market mechanisms and the role of clinical evidence are given equal weight in the research.

My objective with the quantitative research was twofold. On the one hand, I wanted to understand as thoroughly as possible the specific market patterns and interpret them within the framework defined in the qualitative research. To do this, I saw the need for both cross-sectional and longitudinal studies that located several European pharmaceutical markets at the focus of the research. On the other hand, I wanted to quantify the impact of the factors that exert a profound influence on drug prescription. To achieve the first objective, I intended to analyse secondary data, while for the second objective I decided to carry out primary marketing research.

The research questions and the methodology together help to achieve the following research objectives:

- To develop a multi-disciplinary conceptual framework suitable for analysing the effect of factors that influence drug use. A literature review revealed that this knowledge is fragmented, both geographically and across disciplines.
- To focus on the importance of clinical evidence and proofs, and employing this perspective to carry out a comprehensive analysis
- To examine the practical applicability of the framework to pharmaceutical management

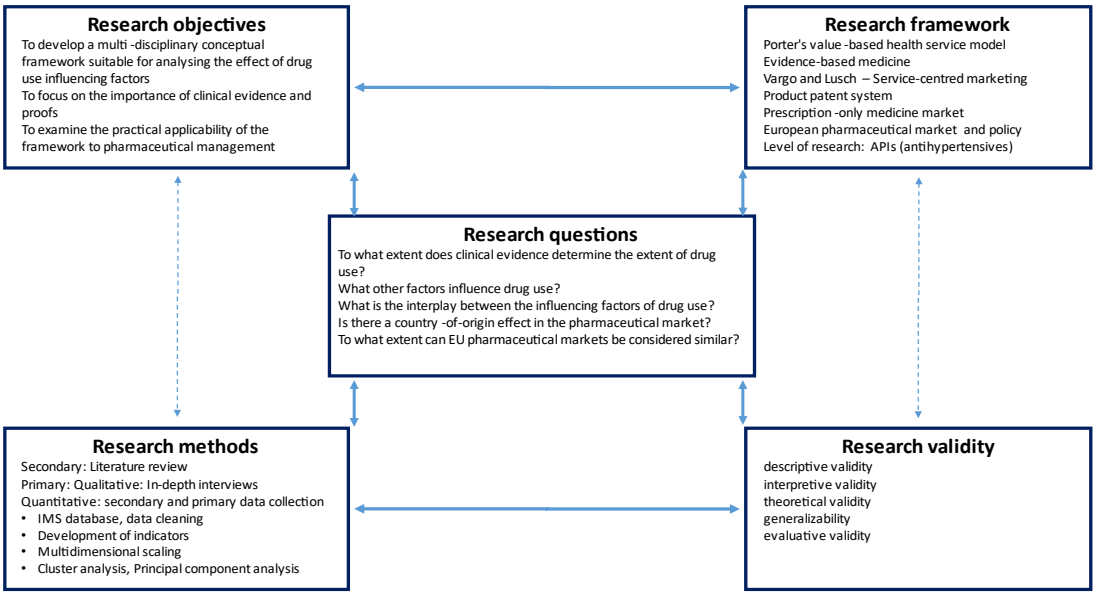


Figure 14 Definition of the field of research according to Maxwell's research model

Defining the research framework precisely is essential for the appropriate investigation of the research questions. The safety and efficacy of pharmaceuticals has been previously defined. Clinical appropriateness is determined by the two effects together. The central thesis of my research is that different drug therapies should be ranked according to clinical appropriateness (EBM). My hypothesis is that, in the long term and under good competitive conditions, the positive attributes of clinically more effective and safer active ingredients should be reflected in the sales of drugs. This may be distorted by country-specific price levels, pharmaceutical policy instruments, the marketing efforts of manufacturers, and the interplay between these factors. Research was carried out in the European pharmaceutical market.

As mentioned previously, together with the objectives, the aim of the research is to analyse relationships at a systemic level, applying a novel approach compared to previous research, and using the examples of several countries. The research framework may be summarized in the following points:

- depth of research: level of active ingredients (APIs),
- research carried out on the market for generic APIs,
- research includes APIs for which the restrictive patent expired at least five years ago,
- no innovative therapy has emerged for the given indication,
- prescription-only APIs are investigated.

3.2. Selection and ranking of the drug therapies under analysis

After the initial research question and objectives had been defined, it was necessary to select a group of therapeutic classes that could meet the criteria defined in the research framework. The research framework was shared with the physicians that were interviewed, and their opinion was sought: the choice was made for examine hypertension drug therapies. ACE inhibitors and ARB therapies meet all the criteria described in the introduction as they are predominantly prescribed for the same indication. No additional exclusion was necessary between the active ingredients at the intra-class level. As no physician was involved in the initial phase of the study, the ranking that resulted from the literature survey was validated by physician peers later. Thereby, I intended to confirm the validity of the research. (Appendix 6 includes the details of physicians involved in the selection of the therapeutic area.)

While the validation was incomplete, market data were neither collected nor analysed to ensure that assessment remained impartial. From a medical point of view, the use of ARBs is recommended over ACE inhibitors due to their more favourable side-effect profile. Figure 15 (below) shows the clinical ranking of drug therapies with ACE inhibitors that are used in the later interpretation.

ACE inhibitors	Rami-pril	Enalapril	fosino-pril	Lisinop-ril	Perindo-pril	Zofeni-pril	Capto-pril	Trando-lapril	Benaze-pril	Quina-pril	Moexi-pril
Clinical Rank	1	2	2	2	2	2	3	4	5	5	5

Figure 15 Summary of relationships between clinical evidence

3.3. Research methodology

The first phase of my research was defined by exploring the possibilities and identifying dimensions described by Maxwell that are relevant to my research. In doing so, the field of my research could define the research framework, the key questions, the objectives, and the associated methods in an integral way. Each of these dimensions has evolved considerably over the years. Fundamentally, the research has grown out of the research question to what extent it is true that patients receive the clinically most appropriate drug therapy? A further question is linked to the previous one (what other factors might distort this relationship?), followed by the question of how this could be investigated and generalized in a methodologically adequate way. Obviously, the first stage of exploring possibilities involved a literature review and qualitative research, including expert interviews. Expert interviews with physicians confirmed the choice and ranking of therapeutic classes, and then, with the use of qualitative methods, a complex set of relationships was explored and constructed to explain the interplay between clinical appropriateness and market performance in drug-purchasing decisions. This framework also forms the basis for my marketing research.

3.3.1. Qualitative research methodology. Analysis of factors influencing market performance—the path from clinical evidence to use of drugs

3.3.1.1. The second and third phase of qualitative research: basis of the framework

Following the selection of therapeutic classes, I turned again to experts and, through structured interviews, sought their views on the questions, findings, and research

framework defined up to that point. (Appendix 2 describes the structured interviews and the name and the position of the experts thereby interviewed.) Experts were selected through snowball sampling. At first, I consulted colleagues working in strategic marketing, and then in consultation with them additional interviewees were selected. I attempted to include people who had multiple perspectives on the functioning of several markets (management and/or analytical positions) and who, I hoped, would be able to focus on the fact that I was not only looking at the functioning of the pharmaceutical industry but also at the impact of clinical appropriateness in relation to different factors.

The structured interviews highlighted the usefulness of limiting the doctoral research to EU pharmaceutical markets and excluding the US pharmaceutical market from the analysis. The main reason for this is that the EU and US pharmaceutical markets and their regulation differ to such an extent that they each deserve a separate study. If the US pharmaceutical market had remained the focus of the research, attention would have been distracted from my main research questions and the purpose of the research. Expert interviews also highlighted that the differences in the regulation of pharmaceuticals in European pharmaceutical markets adds just enough complexity to the interpretation of the field of research. In addition to confirming the validity of the subject and the research questions, the greatest achievement was the identification and clarification of the factors that distort the relationship between clinical appropriateness and market performance during drug prescribing and dispensing in pharmacies, and during the purchasing-decision process. This relationship is presented in the chapter that describes results.

In the third phase of research, I focused on the main determinants of drug prescription, including physicians' perceptions. Structured interviews with peers working in operational marketing helped me to obtain an in-depth understanding of the context. I tried to assign more and more precise concepts and categories to data I collected during the expert interviews. Once the concepts were clarified, I tried to make connections between the category and its dimensions. Throughout, I was careful not to lose my focus on the interplay between clinical evidence and market performance. The main difficulty was ensuring that the research framework would be distorted during the interviews through emphasizing that interviewees should focus on the analysis at the level of active ingredients. It was clear all along that, being aware of the current operating model of the pharmaceutical industry, the focus should be on the prescribing physician. (Appendix 3 describes the structured interviews, the name and the position of the experts interviewed.)

3.3.1.2. The fourth phase of qualitative research: framework finalization

The continuous development of theory led to the fourth phase of the research. In the qualitative part of the work, I used open coding to develop categories, and then partial axial coding to explore the relationships and to group the previous codes. The concepts, the concept-based categories, and the interrelationships between them were thus clarified. Factors that determine the relationship between clinical appropriateness and market performance were arranged into a logical chain, and through re-reading the interview drafts, a new system of codes emerged. In the results section of the dissertation, I attempt to draw conclusions from the primary research results and reinterpret the codes to present a theoretical structure of the studied relational system (I consider clinical appropriateness to be universal and investigate its role in pharmaceutical decision-making). By contextualizing the categories that were the outcome of open coding, the following factors were considered:

- What is the causal relationship between the factors? How can the set of factors be arranged into a logical chain?
- At what level does each factor exert influence on the complex set of relationships?
    - I: The impact of a certain factor can be interpreted at the level of active ingredients when the interplay between clinical appropriateness and market performance is examined
    - B: The impact of a certain factor can be interpreted at the level of brands when the interplay between clinical appropriateness and market performance is examined
    - M: The mixed impact of a certain factor—that is, interpreted at API level and brand level—can be explained when the interplay between clinical appropriateness and market performance is examined
- What level of interest is behind the effect of a particular factor? (In explanation, it is important to note that the factor may appear at the level of the active ingredients, but the manufacturer's interest in the impact exists at the level of the brand.)
    - I: API-based interest is behind a particular factor when the interplay between clinical appropriateness and market performance is examined
    - B: Brand-based interest is behind a particular factor when the interplay between clinical appropriateness and market performance is examined

    - M: Mixed (API and brand) interest is behind a particular factor when the interplay between clinical appropriateness and market performance is examined
- How can the impact of a particular factor be interpreted in the framework under consideration?
    - R: Reinforcing: The factor reinforces the impact of clinical appropriateness on evolving market performance
    - D: Potentially distorting: The factor has the potential to distort the impact of clinical appropriateness on evolving market performance
    - N: Neutral: Although the factor may have influence on the issue under consideration, the effect is either insignificant or the resultant effect is expected to be neutral.
- As for marketing mix elements, which factor can be associated with which element of the mix (product, price, place, promotion)

Primary research conducted during the qualitative part of the work did not reach the limit of theoretical saturation. The primary reason for this was that interviewees, although professionals with very different and long experience, were mainly peers from the same company. Nonetheless, I believe that the results of the primary qualitative research and the literature review provide an opportunity to formulate a theoretical framework.

3.3.2. Quantitative research methodology

In the doctoral research, two types of analysis were conducted on secondary market data and primary marketing research to complement the analysis. On the one hand, two effect classes (ARB vs ACE) were compared, and the active ingredients of ACE inhibitors were also compared based on sales volumes and sales revenues for each country on the other. At first, cross-sectional quantitative research was carried out based on sales figures from 2016, and then, looking at the diffusion of innovation, the period between 2001 and 2016 was investigated in relation to both research questions. Finally, the research was complemented with data for 2018 and 2021. Primary marketing research provides deeper insight into physicians' perceptions and thus allows the researcher to conduct an in-depth analysis of prescription-influencing factors and to quantify their effects.

3.3.2.1. Market data used for the analysis

Market performance information was obtained from the IQVIA Health MIDAS database provided by Gedeon Richter Plc. At the first level of research, distribution by

pharmaceutical form was investigated. Since 99.9% of ACE inhibitors and almost 100% of ARBs are used orally, that is, per os, worldwide, subsequent research was limited to per os drug forms only. Investigation was also made at various levels—therapeutic class/country, API/country, and API/country/brand—for the respective markets. The first comparative study was a cross-sectional one for 2016. Further analyses were undertaken using quarterly aggregated ACE inhibitor and ARB sales data for the period between 2001 and 2016, broken down into from two-year to five-year periods. With a study of a duration of 15 years, the aim was to examine changes in market performance at the API level over a longer time horizon and to provide a descriptive analysis of the diffusion of drug therapies and the deciding factors.

The analysis covered nine countries (France, Germany, Hungary, United Kingdom, Spain, Italy, Poland, Romania, and the Netherlands; data for the latter were only available from 2004 onwards). The countries were selected, as discussed in the literature review, after macro-level market data had been investigated. Data were retrieved for the main class of C09 ATC according to brand and mechanism of action, thus research included the two classes of mechanisms, both single-ingredient drugs and combined drugs with other APIs (codes C09A and C09B, as well as codes C09C and C09D ATC4). To capture pharmaceutical sales, manufacturers' revenues (thousand EUR, million HUF) and sales volumes (thousands of 'units', CU; that is, counting units: tablets, capsules, sachets, etc.) were taken into account in subsequent calculations. For comparability, sales volume data were analysed for the countries concerned: more precisely, market shares in percentages were compared which describe the market performance of each API in the countries under investigation.

It was also considered that APIs differ in terms of defined daily dose (DDD) and that different strengths are available. The number of days of treatment (DOT) is only known when all the information on APIs is available. Information on sales volume (thousands of tablets) was obtained from the IQVIA database. To correct the dosage differences between compounds, the daily defined dose (DDD, the assumed average daily maintenance dose for a drug used as a main indication in adults) was calculated based on the WHO-published DDD data and the DDD correction, then DDD correction was applied to sales data (Spurling et al., 2010; Tan et al., 2006). Calculations were undertaken on these data to reveal whether the sales volume (later CU/MAT) ratio was linearly proportional to the DOT. It was confirmed that the values used in the analysis represent the DOT ratio of therapies.

For combination products (e.g., lisinopril amlodipine), DDD was defined as the number of pills to be taken every day according to the C09 ATC major class. Combination products are described by WHO as being characterized by a once-daily dose regime, and therefore the DDD of combinations is considered to be uniformly equivalent to the number of drugs sold. Sales data that were available for each formulation were aggregated at API level for each ATC4 class and quarterly data were summarized annually.

To estimate prices, manufacturer's revenue, and volume (CU) data were used, and prices were estimated separately for DDD-adjusted volumes. This estimate does not provide consumer prices, but the aim was to analyse the aggregate data at API level and to examine the long-term relative market performance of each API in different countries. Since the demand for drugs is the result of decisions made by several actors on the consumer side, it seemed more appropriate to estimate manufacturers' prices of APIs. By analysing clinical and pharmacy sales data, separately recorded in the IQVIA database, data were summarized at product group and API level; that is, both clinical and retail sales data were considered.

Data were processed using Microsoft Excel 2010, Stata IC 13.1, and SPSS Statistics 25.0 software (StataCorp LLC Lakeway Drive, College Station, TX, USA).

To explore relationships, multidimensional scaling and cluster analysis were used to reveal similarities and differences between APIs and between countries based on sales data from different countries. The analysis was further enriched through the visualization of time-series data, a custom indexing methodology was developed for data interpretation and comparison, and a market concentration index was also used.

3.3.2.2. Multidimensional scaling

A multidimensional scaling method was used to illustrate the similarities and differences between countries in a professional way. Multidimensional scaling is a method of comparing objects based on their degree of similarity considering several variables simultaneously (Malhotra, 2010). The method can be used to explore the structure of data by using the similarity measures of objects to represent objects in a low-dimensional space based on the distance between points. The method has the advantage of producing a graphical representation that illustrates the magnitude of the differences between objects, showing which objects are close to each other, and the goodness-of-fit test is done using R2 and stress indices. The method does not provide a direct means of interpreting the relationship between the dimensions of the perceptual space and the

attributes of the objects, but the interpretation can be supported in several ways: by expert interviews, or other qualitative evaluations, or by making additional calculations such as regression analysis to fit attribute vectors to the perceptual space. In this way, multidimensional scaling can be used to identify which objects are close to each other and which are more distant, and to provide clues as to which attribute dimensions form the basis for the spatial location of objects (Backhaus et al., 2015). As for the analysis, countries are located as objects in the multidimensional space, and similarity data are derived from their attributes.

3.3.2.3. Factor analysis

Factor analysis is a technique used to reduce a large number of variables to fewer factors. This multivariate statistical method is used to describe the variability between observed, correlated variables in a potentially smaller number of unobserved variables that are called latent factors. Factor analysis seeks correlated variables in response to unobserved latent variables. Observed variables are modelled as linear combinations of potential factors plus 'error' terms, so factor analysis can be seen as a special case of modelling measurement error in explanatory variables. In simple terms, the factor weights of a variable quantify the extent to which the variable is related to a particular factor.

Basically, two approaches are usually applied:

- Exploratory Factor Analysis (EFA): The assumption is that any indicator or variable can be associated with any factor. This is the form of factor analysis most often used by researchers and is not based on any previous theory—this approach is used in this study.
- Confirmative Factor Analysis (CFA): This is used to determine the factor and factor weights of the measured variables and to confirm what is expected from the underlying or prior theory. CFA assumes that each factor is associated with a specific subset of the measured variables.

In factor analysis, the method of principal component analysis, the method most commonly applied by researchers, was used to extract factors. Principal component analysis attempts to explain as much variance as possible using the first factor, then removes the variance explained by the first factor and continues with the second factor, a process that continues until the last factor.

Rotation can help to make the results easy to understand. The eigenvalues do not affect the method of rotation, but rotation does affect the extracted eigenvalues or the percentage

of variance. Several rotation methods are available: No rotation, Varimax rotation, Quartimax rotation, Direct oblimin rotation, and Promax rotation. Of these, Varimax rotation was used, ensuring that the resulting factors are orthogonal (that is, uncorrelated).

3.3.2.4. Cluster analysis

Cluster analysis is a multivariate method used to classify a sample of subjects (or objects) into a number of different groups based on the set of variables being measured, so that similar subjects are placed in the same group. There are several different methods that can be used to perform cluster analysis, but in this study the following hierarchical methods were used.

- Nearest-neighbour method (single connectivity method). With this method, the distance between two clusters is the distance between the two nearest members or neighbours. This method is relatively simple but is often criticized because the structure of the cluster is not taken into account, and this can lead to a problem called chaining, which may result in long and heterogeneous clusters. However, it is better than the other methods if the natural clusters are not spherical or elliptical.
- Farthest Neighbour Method (full connectivity method). In this case, the distance between two clusters is the maximum distance between members—that is, the distance between the two farthest subjects. This method generally produces compact clusters of similar size, but, similarly to the nearest neighbour method, the structure of the cluster is not considered.
- Ward's method. With this method, all possible cluster pairs are combined and the sum of squared distances within each cluster is calculated. This is then aggregated to all clusters. Finally, the combination that gives the lowest sum of squares is selected. This method produces clusters of approximately equal size, which is not always desirable. It is also quite sensitive to outliers.

To measure the distances, we used Euclidean distance for the nearest and furthest neighbour models, and Euclidean squared distance for Ward's method. Both multidimensional scaling, factor analysis, and cluster analysis were undertaken using SPSS Statistics version 25.0.

3.3.2.5. Index numbers used in the analysis

Derived index numbers were developed for the research to describe the markets:

- Price level of ARB and ACE inhibitors: The proportion of sales revenue to sales volume. Price levels of countries by therapeutic classes.
- Price level difference index (ratio of ARB price level to ACEI price level): The ratio of the average price level of ARB to ACE inhibitor therapies shows how much more ARB therapies cost compared to ACE inhibitors in each country. Calculation: the ratio of manufacturer's sales revenue to sales volume for ARBs and ACE inhibitors.
- Volume difference index (ratio ARB volume to ACEI volume): The ratio of ARB sales volume to ACE sales volume. The value shows the ratio of ARB sales to ACE inhibitor sales for a given country. Calculation: ratio of ARB sales volume to that of ACE inhibitors.
- Sales volume index (ratio of ARB sales volume to ACEI sales volume): Ratio of sales revenues. The value determines the ratio of expenditures (consumer and financier) for ARB to ACE therapies. It can also be interpreted as the product of the volume and price level difference index. Calculation: ratio of manufacturer's revenues of ARB to that of ACE inhibitors
- ARB reference pricing: The sales revenue index (in which volume and price play a role) multiplied by the volume difference index. The significance of the volume is thus weighted squarely and it is also taken into account how much of a higher sales volume of ARB therapy can be achieved compared to that of ACE therapies.

In addition to the derived indices, market concentration was described by Hirschman's concentration index (HHI).

3.3.2.6. Changes of ACE inhibitors and ARBs sales data over time

In the analysis of changes in sales data over time, both combination and single-ingredient drugs were considered. For this analysis, indices were created using data for the years 2016, 2009 and 2001, as described above, and multidimensional scaling was used to facilitate data visualization. Finally, the presentation of trends was complemented with the most recent data (2021), albeit only descriptively.

To explore the specific features of time series, the annual manufacturer revenues for the entire C09 ATC class were plotted based on the entire DDD-corrected dataset that was available; furthermore, the relative market share of ARBs to ACEIs, and the average price of ACE inhibitors and ARBs were also illustrated over time.

Three Central and Eastern European countries (Hungary, Poland, Romania) and three Western European countries (France, Germany, and the UK) were included in the analysis of ACE inhibitor therapies. The selection was based on the results of the 2016 cross-sectional study due to the following arguments. The countries in the Eastern European group were characterized by a relatively low market share of ARBs, but also by a split in preference for ACE inhibitors. The latter group was characterized by most typically using ramipril from all ACE inhibitors, albeit with a different weight and differences in the market share of ARBs were also found.

During this phase of the research, understanding prescribing preferences for these APIs was a central goal. Therefore, only pharmacy sales data were used, excluding hospital prescriptions (regarding hospital prescriptions, central drug purchasing considerations may override prescribing decisions). Time series of aggregate data for single-ingredient and combination drugs of ARB and ACE inhibitors, as well as API-level market data, were plotted graphically. Further time-series visualizations were used to describe market competitiveness in terms of price and number of brands of the same API on the market, thus showing how generic competition is affected by changes in prices and in the number of available substitutes.

Market concentration was measured using the Herfindahl-Hirschman Concentration Index (HHI) to describe the market concentration for active ingredients of ACE inhibitors each year. The HHI index was also used to measure the relative market share of ACE inhibitors and non-DDD adjusted data to show the relative turnover of the combination of dosage units (tablets, capsules, etc.).

The price and number of brands of the same API present in the market at the same time were plotted to illustrate the competition in the market. A dramatic decrease in prices and an increase in the number of available substitutes is a good indicator of the beginning of generic competition. The Herfindahl-Hirschman concentration index (both DDD and non-DDD adjusted HHI) was calculated for selected years and plotted as a function of time to describe the concentration of ACE inhibitors in the market. The analysis of the relative market share of ACE inhibitors and the HHI calculations for the non-DDD-corrected data provided an overview of the relative sales of each dosage unit (tablets, capsules, etc.), regardless of the dose used.

4. Results

4.1. Results of the qualitative research

4.1.1. Result of the first and second phase of the qualitative research

In this chapter, the qualitative research results, the body of knowledge based on expert interviews, are summarized (for details of interviewees, see Appendix 2). Results suggest that the interplay between clinical appropriateness and market performance is indirect, and determined by a combination of several intermediate factors. The research into prescription-only drugs revealed that prescribing *physicians* are the most important actors in the context of relationships. Physicians are *'in the middle of the interactions'* in this set of relationships and *'they make the decision about therapies'* (sales manager). Decisions are made *'on the basis of their experience and knowledge, which is largely determined by information from third parties'* (sales manager). *Clinical literature* is one of the most important sources of their knowledge, and physicians acquire and obtain insight during their studies and their practice. Clinical literature is the source of the evidence that allows for a comparison of drug therapies on the basis of safety and efficacy criteria (also on the basis of evidence-based medicine). Obviously, physicians' information levels vary, but in general, in the context of relationships, *'physicians are the ones who are most concerned with the scientific appropriateness of therapies, and it is also them who, through their studies, have in-depth insight into clinical information on therapies'* (sales manager). It is important to note that *'physicians make decisions based on perceived quality'* (marketing manager), which depend on the level of information and a number of other objective and subjective factors. The primary aim of *pharmaceutical industry players* is to make a profit while meeting patients' needs. To this end, industry players develop and market therapies that help them to achieve these objectives. The clinical appropriateness of therapies is addressed in the generic model in several different ways.

On the one hand, pharmaceutical companies seek to develop therapies that have the greatest sales potential from a medical point of view (and from the originator, the sales point of view). Through their marketing efforts (detailing, PR, conferences, trade journals), pharmaceutical companies supply prescribing physicians with an increasing amount of information and thereby attempt to enhance their perceptions. Although strict regulation is aimed at phasing out abuses, it cannot be ignored that pharmaceutical companies seek to maximize their profits. Due to their capital strength, companies are at the forefront of creating and accumulating scientific information. In fact, they provide the

vast majority of funds for costly clinical trials, thus generating the evidence mentioned before. By increasing the level of information supply, they also exert a beneficial effect, although distorting effects cannot be ignored, such as the institution of ghostwriting (including scientific articles ostensibly written by independent authors but which are in fact backed by pharmaceutical companies). The penetration of ghostwriting into scientific literature is very difficult to detect, and effects are not necessarily always negative. Estimates vary widely from case to case and from therapy to therapy (estimates range from 10–40%, but in some cases ghostwriting rates are much higher – as much as 70%). Therefore, this factor cannot be neglected (Sismondo, 2007). On the whole, *'the marketing efforts of pharmaceutical companies tend to focus on how to allocate marketing expenditures across marketing activities directed towards physicians, patients, financiers, and pharmacies. Complexity is underlined by the fact that this mix varies from country to country, as do pharmaceutical policy instruments and regulation'* (sales manager). Expert opinions suggest that the diffusion of clinically more appropriate therapies should be facilitated by industry players in such a way that a 'paradigm shift' could be brought about more quickly by a larger number of competitors when a genuinely more effective therapy comes to market. This assumption may be distorted by the fact that different countries may consider different therapies to be the 'best'. An important role is played by the therapeutic guidelines (a professional aspect) on which medication is based in each country, and by other principles covered in regulation (e.g., price). As an anomaly, in certain markets companies can shift these proportions if their capital strength or marketing potential is large enough.

Public authorities play a multifaceted role in this framework. Pharmaceutical authorities decide—by examining evidence—whether a particular drug therapy should be granted marketing authorization in their country. For an originator product, the main evaluation criterion is specified in the cost-benefit analysis of the therapy, and as for generic authorization, quality and clinical equivalence of the originator product has to be guaranteed. In most parts of the developed world, drug prices are reimbursed by the state, particularly in the European pharmaceutical markets, and for the hypertension therapies under investigation. The role of public authorities in determining the level of reimbursement is therefore also an important factor, since what patients and physicians perceive as the price is the retail price minus any reimbursement. The amount paid out as reimbursement makes public authorities, as financiers, an important shareholder in the context of relationships. At this point, public regulation comes back into play as an important factor, in this context through the instruments of pharmaceutical policy. As an

authoritative factor, professional and institutional guidelines are also worth mentioning, as they play a very important role in prescribing drugs, also through physicians.

The whole context of relationships concerns *patients*, as the key question is whether patients are receiving the right therapy, although they do not really play a central role in the framework under consideration. A main reason for this is that *'the vast majority of patients cannot judge the appropriateness of a drug therapy for the treatment of their symptoms'* (research director). *'Patients are not the real decision-makers in the consumer decision-making process, but they are able to influence it. They can do this by influencing or overriding physicians' decisions (e.g., not dispensing a drug or choosing a substitute alternative when rules allow it)'. 'For patients, it is more likely a matter of perceived quality based on information they can obtain from the various sources (internet, clinical literature, physicians, word of mouth, press)'* (sales manager). Therefore, most patients do not have the knowledge to objectively evaluate the value of therapies. However, there is a trend for patients to become increasingly knowledgeable in their efforts to influence physicians' decisions. Information is mostly gathered from the internet or from patients' environment. Patients also make financial decisions when buying drugs, so price is also a factor.

The *distribution network* is of less importance in the interplay between clinical appropriateness and market potential. Wholesalers' effects are very indirect (parallel imports, persuasion of retailers) but retailers should not be left out of the equation. Although the impact varies from country to country, pharmacies can influence purchasing decisions. One example is Germany, where ACE inhibitors are subject to so-called 'aut idem' prescription. This means that unless physicians directly state that substitutability is not allowed, pharmacies can override physicians' decision and prescribe a different API of ACE inhibitors to the patient. Furthermore, pharmacies' decisions can be influenced by *patients*' requests, by the *financier* (and the price), and by *pharmaceutical industry players* (pharmacy visits).

The *number of competitors* is also considered when relationships are investigated. Since generic drug therapies are examined at API level, the reason why this is important is that the number of pharmaceutical companies that have launched a product with a certain API is a key factor in prescribing decisions and in pricing. It is easy to understand, for example, that if X alternatives are available for one API therapy, and 2X alternatives for another, then in the second case, ceteris paribus, one would expect a lower price and more marketing messages addressed to physicians.

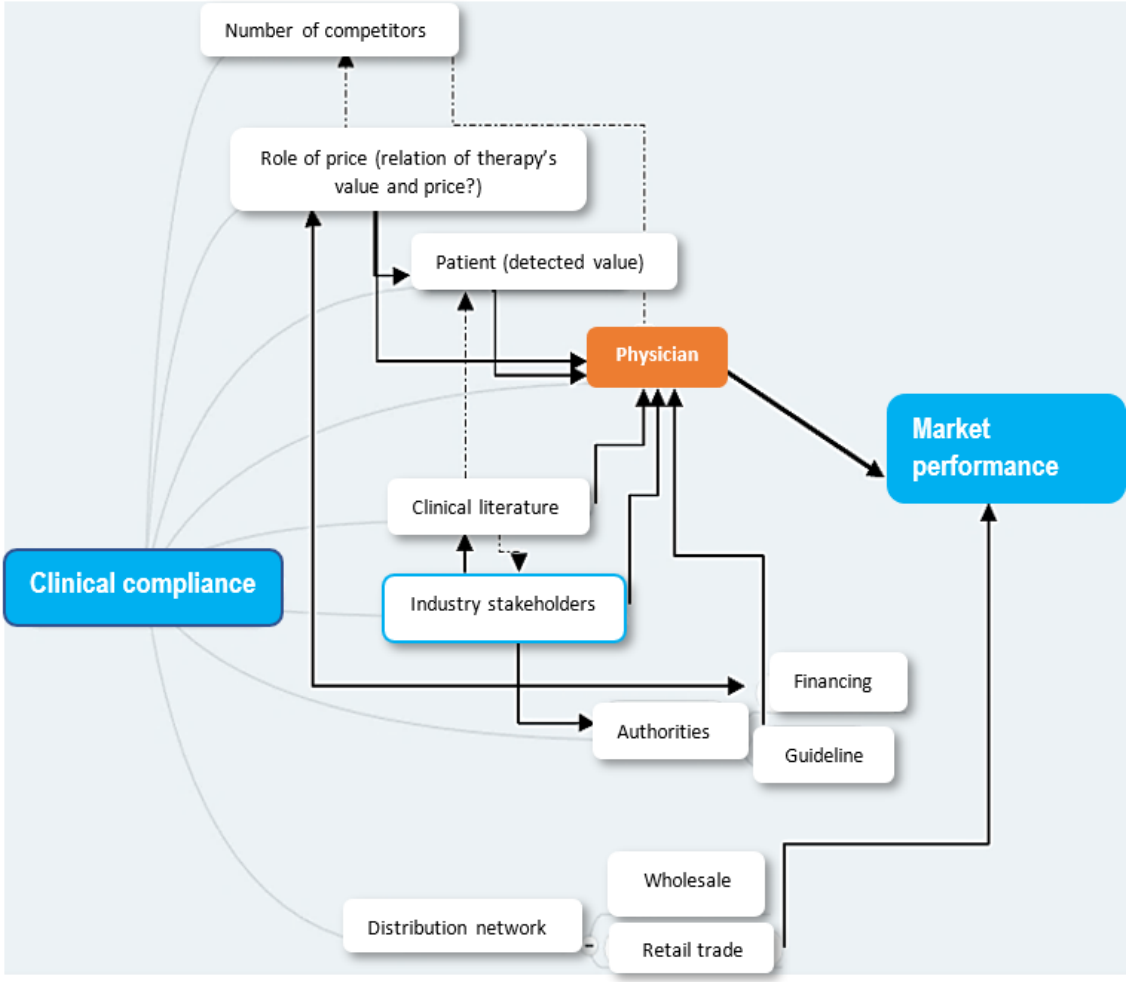


Figure 16 Framework constructed as a result of the first and second phase of qualitative research. Key determinants of the relationship between clinical evidence and market potential

4.1.2. Result of the first and second phase of the qualitative research – physicians' perceptions

For prescription-only drugs, the impact of influencing factors on *prescribing physicians'* decisions was also explored in more depth (based on information from interviewees, as detailed in Annex 3). Both the literature review and the results presented so far suggest that physicians are subject to a myriad of influencing factors and the power of these factors is controversial.

For generic products, two types of marketing communication are distinguished, with varying degrees of activities. According to one type of the latter communication, brand-building is not a common activity. Manufacturers usually give discounts to retailers and pharmacists using non-proprietary names (INN), so due to the higher margins pharmacists will promote the sale of drugs that increase their profit. When appropriate, they may override physicians' decisions and offer a substitute product. The other direction of

marketing communication concerns brand building, with which, among other things, manufacturers intend to increase the number of prescriptions. In this case, the expected result is to be achieved by building on and enhancing good relationships between physicians and sales representatives, and between physicians and the pharmaceutical company (interviews 1 and 2, see Annex 3).

Without exception, interviewees confirmed that the existence of a good relationship between the pharmaceutical company and physicians is the most important issue. The main aim of each marketing action is to have the company's products accepted into the group of products that physicians prescribe (evoked set). This is a very small group, as physicians prescribe drugs from about 1–4 companies, on average, for each therapy. On average, a physician is aware of and can keep in mind about 80 products, from which prescriptions are usually made for all therapeutic classes (Interview 3).

Pharmaceutical marketing has become much more rigorous in recent years due to pharmaceutical industry excesses that have become well known through the media. Nowadays, compliance with strict rules is essential, data must be made public and transparent both in external and internal audits, and all types of marketing efforts must be accountable. At the same time, due to strict rules, marketing budgets have also been decreased. Despite this, pharmaceutical professionals consider the tightening up of marketing communication and the uniform regulation of marketing communication across the industry as a positive development (Interview 1).

In building a good relationship between pharmaceutical companies and physicians, sales representatives play an influential role. Their work and performance can have a powerful impact on the market performance of products. The first and unavoidable step for the success of their work is to create homogeneous groups through good segmentation and market research, and to find the right target groups—and this is not always an easy task. ‘Sales representatives, in the eyes of physicians, have expert knowledge of the product they are promoting, they should know the product perfectly well, and thus it is essential that sales representatives are highly qualified’ (Interview 3). They should impart their knowledge to physicians in a way that physicians feel that their work is improved and supported by sales representatives. Although physicians are aware of the marketing impact of drug detailing, they can get professionally useful information from the right sales representatives, thus they still consider detailing to be the most important source of information (Interview 3). In addition to being experts on a product, the formal business role of sales representatives should be complemented with an informal and direct personal

relationship (Interview 3). Sales representatives must pay attention to three main things during the performance of their job: number of visits, quality of visits, commitment, and motivation during visits (Interview 3). In terms of the number of visits, neither too few visits nor too many is beneficial (Figure 17). On the one hand, products have to be explained to the physician, and this requires regular visits. On the other hand, engaging in too many visits raises the risk that representatives invest too much time and thus too much cost in a single physician, which, above a certain level, leads to no further increase in prescriptions. It is the task of companies to find the optimal balance through the work of sales representatives: when the optimal frequency of detailing results in an optimal number of prescriptions.

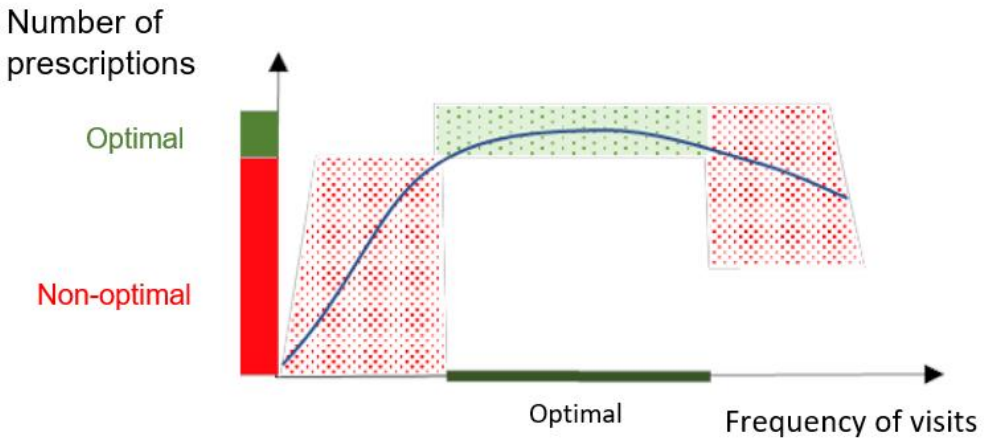


Figure 17 Relationship between frequency of drug detailing and prescriptions (Source: author's construction)

Sales representatives should also strive to make good use of quality time during their visits as they usually have to promote multiple products (up to 6–8 during one visit). On average, physicians are able to devote 60% of their attention to the first product, and then their attention begins to decline rapidly and exponentially, leaving only 30% for the next product. During this short period of time, while marketing communication is being carried out, pharmaceutical representatives attempt to convey valuable information to maintain attention, emphasizing product benefits, drawing attention to context, and reinforcing physicians' perceptions (Interview 3). Finally, the state of representatives' motivation and determination during the visit is also a decisive factor. Their work can be evaluated according to three criteria: the input they put into their work, the output that quantifies the sales of products, and the expertise and added value they add to their work (Interview 3).

To develop a good professional relationship with physicians, the pharmaceutical industry sponsors congresses, conferences, professional training programmes, and other social events for physicians. These events are professional ones: medical content can easily be delivered, the main message of products can be conveyed to participants, and physicians willingly participate in these events because they feel that by doing so they can develop in their profession. At international events, companies also provide translation and interpretation services for those who need this. These small gestures are all signs of a good relationship (Interview 1).

Although professional contact with sales representatives is important, it is necessary to undertake other marketing activities to support sales revenues. Factors that most influence drug choice are the efficacy and the safety of products, but other product attributes can also affect physicians' final choice (Interview 1). These include the size of the product, the form in which patients can take the drug, the packaging of the product, etc. The role of marketing is to find a niche market that still offers novelty—for example, antihypertensives currently fall into the 'cash cow' category—but which succeeds in boosting the market by emphasizing combinations (Interview 2). Antihypertensives (e.g., ACE inhibitors) are usually branded, but because many physicians prescribe these APIs extensively, differentiation is essential. 'In brand building, the products are endowed with attributes "as if they were human"' (Interview 1). Expressive elements are used to shape visuals to match the positioning of products. Logo fonts are predefined, and visuals include the name of the API, a tag, and description of the brand essence (which is 1–2 words long). The product is accompanied by a predefined, one- or two-line slogan that is designed to support its positioning. Predefined colours are used for all marketing communication elements of the product; additionally, marketing communication is consistent in style, structure, and colour scheme. All brand elements are associated with the product. The more these motifs are repeated in as many forms as possible, the more physicians remember the product, and thereby physicians' perceptions are affected (Interview 1). Obviously, as market conditions change, so does product branding, in line with the product life cycle, and it is the task of marketing professionals to follow these changes and to address and adapt to market conditions (Interviews 1 and 2).

The timing of market entry, part of the marketing communication strategy, is a critical factor in building market share. Interviewees hold the view that from the moment an API is ready to enter the market, product promotion should start within the first six months.

Furthermore, it is part of the strategy to have a strong and large team of sales representatives to ensure market coverage (Interview 2).

In developing price strategy, manufacturers aim to maintain the widest possible patient care, while complying with the law, and to optimize patient access to drugs; further, to strive to associate added value with their products (Interview 2).

'Regarding drug prescription, physicians appreciate stable manufacturers [ed.: e.g.: a stable supply chain] because stable products are more suitable for patients, thus stability is a valuable feature in terms of patient safety' (Interview 2).

The opinions of interviewees about the country-of-origin effect were slightly variable—for example, 'In Hungary it can be an issue if the product is a Hungarian one' (Interview 1). There is a tendency in certain countries (such as Russia) to prefer local manufacturers. According to interviewees, there is no preference for local manufacturers (for example, in Hungary), but the country of origin tends to influence the building of a good relationship (Interview 2). All in all, information obtained from interviewees indicates that the country of origin has no direct effect, but an indirect effect is very likely.

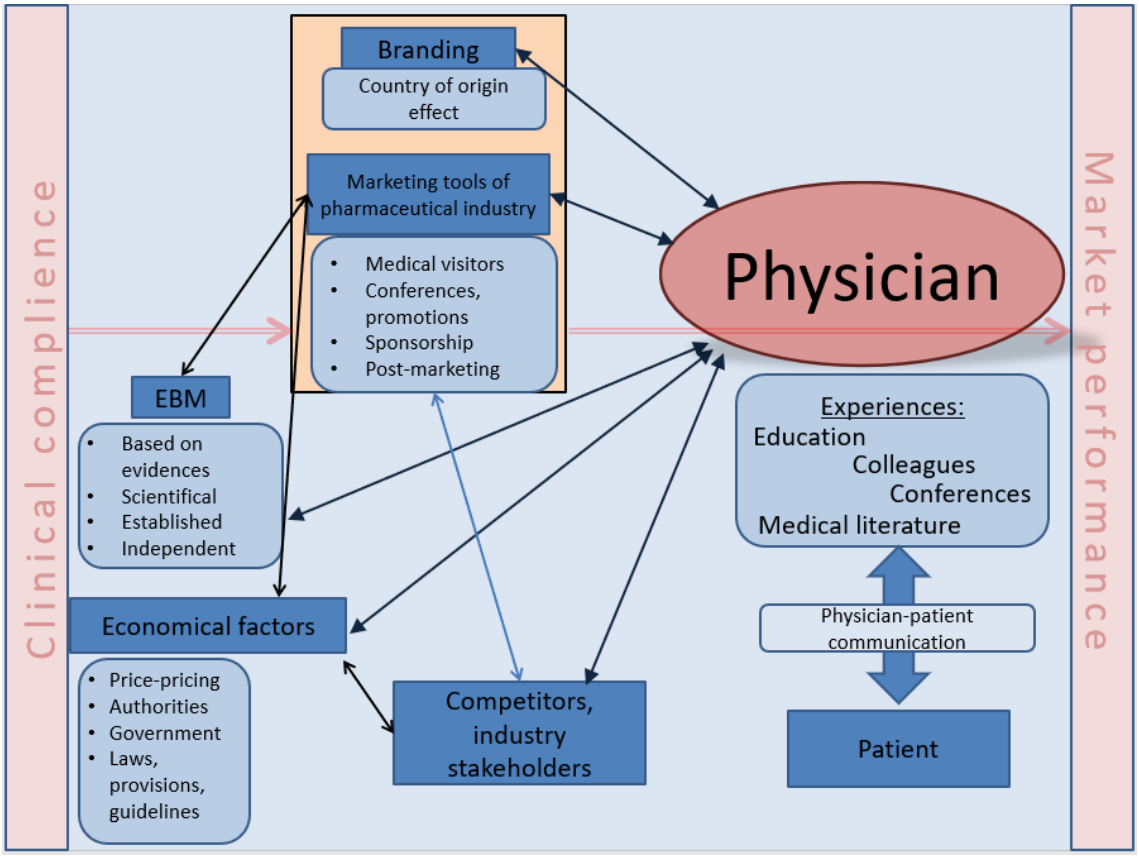


Figure 18 Factors that influence physicians' choices in the framework of clinical appropriateness and market performance

Factors influencing physicians' prescribing behaviour, based on the literature review and interviews, are illustrated in Figure 18. Physicians' perceptions are influenced by a number of factors. However, the power of such factors can vary, both from country to country and at the product level.

4.1.3. Context of relationships between the main determinants of drug use

Based on the qualitative research results, a framework was construed (see Figure 19, below). In relation to this doctoral research, creating a framework is a major achievement, with the help of which I seek to develop a new multidisciplinary interpretation of the theories that have guided the research and to explore the relationship between clinical appropriateness and market performance by combining evidence-based medicine with the marketing approach. The coding of the levels (a hitherto unexplored element) at which each factor exerts its effect (API/brand/mixed) is included; furthermore, what interests are behind the effects and what the direction of such effects are (enhancing, distorting, or neutralizing the impact of clinical evidence).

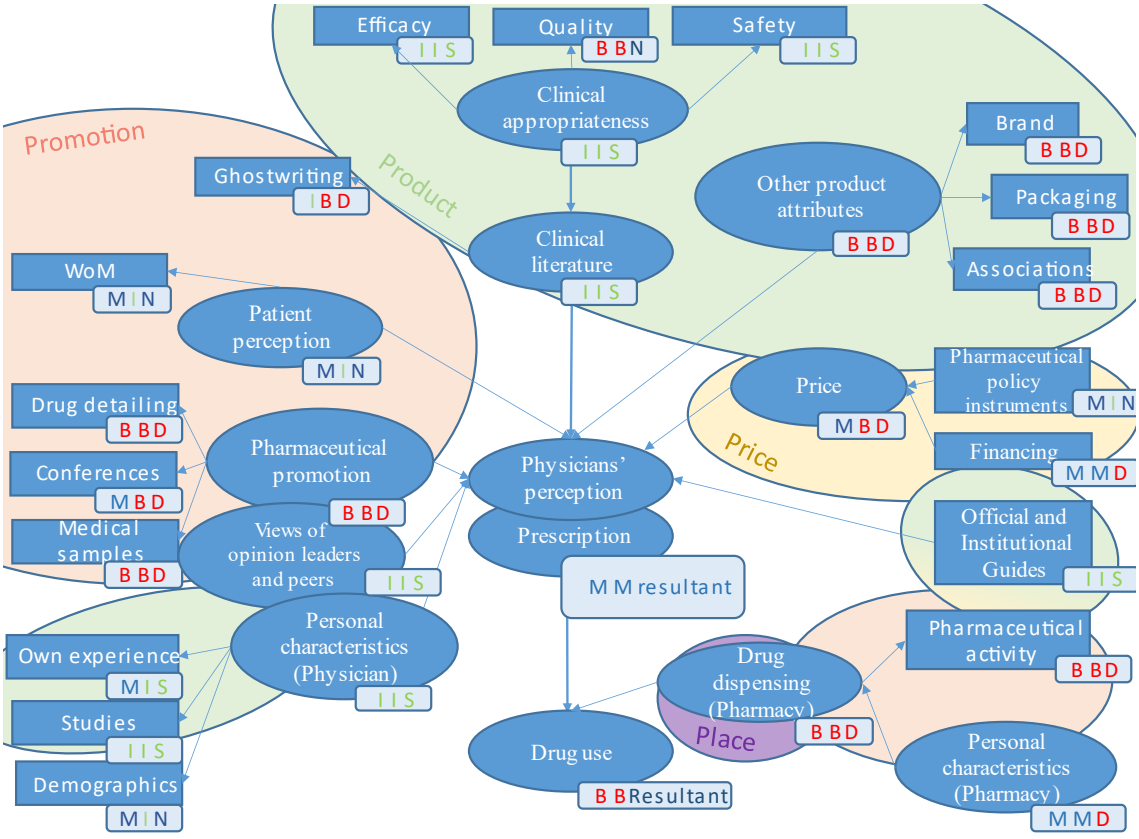


Figure 19 Context of relationships between the main determinants of drug use and the impact of clinical appropriateness on each factor (explanation for the level of impact, the underlying interest, and the direction of impact)

Results revealed that clinical appropriateness can play a role almost without exception for all factors in relation to determining sales at the API level, but this latter factor is by no means the sole or dominant factor in the complex set of interrelationships that make up purchasing decisions in the pharmaceutical industry. Since the conditions for perfect competition are far from existing (e.g., a small number of competitors due to barriers to entry, imperfect information supply), physicians' perceptions of clinical appropriateness and the resulting prescription and subsequent drug purchases in pharmacies may be distorted at many points and by many actors and factors. Interviewees also believe that it is highly likely that clinical appropriateness, the most significant factor, is distorted by 'noise' and can only be seen in the anomalous sales figures, if at all. Based on the experience obtained from the interviews, information was coded, and the research results are shown in Figure 19.

The figure attempts to illustrate the large number of influences on drug prescribing, dispensing, and consumption decisions. The impact of clinical appropriateness as a key product attribute prevails differently in the outlined framework. The letters next to each factor indicate the following:

1. At what level does each factor exert influence? (I: API; B: brand; M: mixed)
2. What interests are behind the effects (I: API; B: brand; M: mixed)?
3. What is the direction of the effect (S: strengthening clinical appropriateness; D: potentially distorting; N: neutral)
4. To which element of the marketing mix does the factor belong?

A clear pattern emerges that clinical appropriateness, a key product attribute, can only be leveraged if the impact is understood at the API level. Once a factor starts to exert influence at brand level, potentially distorting effects emerge. This is a particularly interesting issue when the role of product attributes in the marketing mix is investigated. The figure shows that, apart from clinical appropriateness at the API level, the other product attributes—which can be interpreted at the brand level—already have potentially distorting power. The figure is not intended to suggest that pharmaceutical and retail actors with a business interest only have a distorting effect on the relationships, but I think it is important to highlight that the business and economic interests both of public and business actors can influence the use of drugs if based on clinical data alone. From a marketing point of view, this result reveals the factors that industry players can take

advantage of to exert considerable influence on drug prescription. Awareness of the factors included in the framework of the qualitative research and their interaction with each other provides a basis for an in-depth analysis of the quantitative research results and a valid interpretation of the patterns that emerge. The outlined interrelationships show how multidisciplinary consumer decision-making in the pharmaceutical industry is, and what an interesting arena it is in which business, social, and professional interests can meet.

4.2. Results of the quantitative research

The results of the research are presented according to the following logic:

- Results of the cross-sectional analysis in 2016:
    - Comparison of the two API classes (ARB vs ACE)
    - Comparison of the market performance of ACE inhibitors—Description of each API and the countries under study
- Changes in the market diffusion of APIs during the period when API therapies become generic (between 2001 and 2016, additional analysis for ACE therapies between 2012 and 2018, cross-sectional analysis in 2021)
    - Comparison of the two API classes (ARB vs ACE)
    - Comparison of the market performance of ACE inhibitors—Description of each API and the countries under study
- Primary marketing research and its results aimed at quantifying the impact of influencing factors on prescribing decisions and comparing marketing research results with real market data.

4.2.1. Results of the analysis in 2016

4.2.1.1. Comparison of market performance of ACE and ARB therapeutic classes

Clinical research has proved that ARB therapies are considered clinically more beneficial than ACE inhibitors. Table 10, below, is a comparison of the market patterns in the studied countries based on the average price levels, sales volumes (CU), and sales revenues (EUR) of the therapeutic classes and on the indices described in the methodology chapter.

Table 10 Comparison of ACE and ARB therapies based on data from 2016

Country	ARB price level (EUR/ CU)	ACE price level (EUR/ CU)	ARB CU (ARB/ Gros) %	ARB EUR (ARB/ GROSS) %	ACE CU (ACE/ GROSS) %	ACE EUR (ACE/GROSS) %	Price level difference index ARB:ACE	Volume difference index ARB:ACE	Sales revenue difference index ARB:ACE	ARB pref. index
ES	0.322	0.064	**41.91**	78.41	58.09	21.59	5.03	0.72	**3.63**	**2.62**
DE	0.158	0.025	32.58	75.56	67.42	24.44	6.4	0.48	**3.09**	**1.49**
FR	0.196	0.147	**49.59**	56.81	50.41	43.19	1.34	0.98	1.32	**1.29**
IT	0.249	0.14	**43.2**	57.53	56.8	42.47	1.78	0.76	1.35	**1.03**
NL	0.067	0.036	**38.87**	54.12	61.13	45.88	1.85	0.64	1.18	0.75
UK	0.138	0.054	29.05	51.26	70.95	48.74	2.57	0.41	1.05	0.43
HU	0.113	0.067	29.22	41.12	70.78	58.88	1.69	0.41	***0.7***	***0.29***
RO	0.143	0.076	25.73	39.4	74.27	60.6	1.88	0.35	***0.65***	***0.23***
PL	0.133	0.085	24.22	33.23	75.78	66.77	1.56	0.32	***0.5***	***0.16***

Abbreviations: FR–France, DE–Germany, HU–Hungary, IT–Italy, NL–The Netherlands, PL–Poland, RO–Romania, ES–Spain, UK–United Kingdom

Multidimensional scaling was used on data to help interpret the results of the table. The method is suitable for examining how similar the nine European countries are in terms of market data for ACE and ARB therapies. A two-dimensional dot chart depicting the relative position of the nine countries was obtained by running the ALSCAL routine in the SPSS Statistics 25.0 software package, and standardizing the variables using a Euclidean distance function and ordinal scaling. The stress index for the fit is 0.00198 (Kruskal's stress formula), and rsq is 0.999, indicating an extremely close fit.

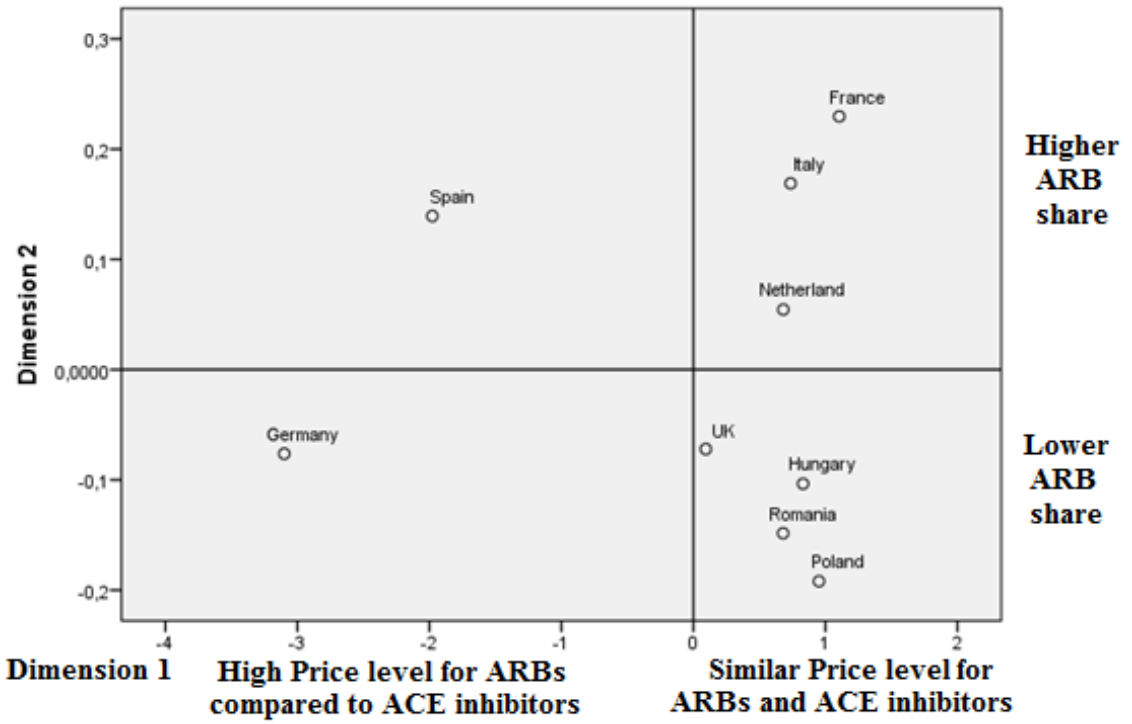


Figure 20 Results of multidimensional scaling on market data of ACE and ARB therapies

The countries on the extended plane can be perfectly evaluated using a 2x2 matrix. The first dimension is determined by the difference between the price levels of ARBs and ACE inhibitors, while the second dimension is mostly determined by the market share of ARBs. Of all the countries, only the UK is difficult to classify into one of the four groups. The reason for this is that although it has a relatively small share of ARBs (29.05%, close to the Hungarian figure), these are achieved at a higher price level. This higher price level is, however, far below the figures found for Germany and Spain, where a considerable difference can be observed between the price levels of the two therapeutic classes (difference of multiples of 5.03 and 6.4). As described, the point representing the UK is close to the origin of the coordinates that represent the centre of gravity of the countries. The value of ARB preference indexes produces a similar pattern. The Spanish market is ranked first, with a large sales volume (41.91%) even at an exceptionally high ARB price level. Germany, France, and Italy form a trio with values between 1 and 1.5. The high sales volumes in the French and Italian markets are supported by lower price levels. The German market, although underperforming in terms of volume, achieves sales at a high price level. Despite the high price level, sales volumes are still higher than in the low-share countries in the next group (32.58%). The Dutch market can be considered average in every respect, while the UK market with its small market share (despite the higher price level) is positioned near the final group. This last group is made up by the Hungarian,

Romanian, and Polish markets. These countries are characterized by a low share of ARB sales (between 24.22% and 29.22%), combined with a price level close to that of ACE inhibitors.

4.2.1.2. Consumption patterns of ACE inhibitors in the studied countries in 2016

Of the two therapeutic classes, ACE inhibitor therapies were also analysed at the API level. In the table below (Table 11), alongside the name of API, the clinical ranking that resulted from the analysis is listed first. This is followed by sales volume data at the API level in the studied markets. The results of the IQVIA database, following a search for API at the country level, were converted into market shares for comparability. APIs with a market share of above 10% are indicated in bold, and the share of the most used API in each country is underlined. The innovator of each API is indicated in the table and, if the innovator of the API (or the compound) arises, the name of the acquiring pharmaceutical company and their nationality is indicated.

Table 11 Market data for ACE inhibitor therapies in Europe

API	Clinical Rank	Sales Volume CU MAT/6/16 (%)									Innovator	Country
		UK	DE	NL	FR	IT	ES	HU	RO	PL		
ramipril	1	**58.8**	**72.1**	5.4	**46.1**	**60.0**	**17.6**	**33.0**	**18.5**	**54.8**	Hoechst >Sanofi	DE, FR
enalapril	2	5.1	**15.9**	**30.7**	5.5	**15.4**	**66.7**	**17.3**	**28.4**	**12.1**	Merck	USA (DE)
fosinopril	2	0.1	0.2	5.9	1.3	1.1	0.5	1.9	3.5	-	Bristol-Myers Squibb	USA
lisinopril	2	**22.9**	9.0	**23.9**	3.3	5.3	6.1	3.3	6.5	5.9	Merck >Astra Zeneca	UK, SE
perindopril	2	**11.9**	0.1	**28.2**	**37.5**	6.8	0.9	**37.1**	**23.2**	**12.9**	Servier	FR
zofenopril	2	-	-	0.4	0.8	*8.0*		-	*5.4*	1.6	Menarini	IT
captopril	3	0.6	1.9	2.8	1.4	0.6	4.5	*5.7*	*7.3*	*5.2*	Squibb	USA
trandolapril	4	0.3	0.0	-	2.4	0.1	0.1	0.3	0.5	1.2	Abbott	USA
benazepril	5	-	0.4	0.0	0.9	0.9	0.3	0.2	0.2	0.4	Novartis	CH
quinapril	5	0.3	0.3	2.6	0.7	1.2	0.8	1.2	*6.4*	3.1	Pfizer	USA
moexipril	5	0.0	0.0	-	0.0	0.1	-		-	-		

The analyses of ACE inhibitors revealed that within the therapeutic class the sales of four compounds are most significant. Ramipril, enalapril, lisinopril and perindopril account for 76.6–98.8% of sales in the studied countries. In general, these APIs have a high clinical ranking (1st and 2nd) from all ACE inhibitors, but shares vary between countries. Another positive result for patients is that ramipril, which has the highest clinical ranking, is also number one in terms of volume share in five of the nine countries (UK, DE, FR, IT, PL). Additionally, fairly high sales figures were also achieved in Hungary (33%). The market share is modest in Spain (17.6%) and in Romania (18.5%), while that of the Netherlands (5.4%) lags behind. Ramipril was developed by the German Hoescht, which was bought up by the French Sanofi group.

Enalapril (developed by Merck, USA, with German roots) is the most popular hypertension therapy by sales volume in the Netherlands (30.7%) and in Spain (66.7%), and accounts for a significant share in other countries, except for the UK and France.

Lisinopril is used in significant volumes in hypertension treatments in the studied countries: in the UK (22.9%), and in the Netherlands (23.9%). The original developer is Merck (USA), but the API is marketed by AstraZeneca (UK, SE). Based on previous research (not detailed in this PhD thesis), it is interesting to note that, looking at the US pharmaceutical market, lisinopril led the sales of ACE inhibitors with a share of over 77% in 2016.

Perindopril has achieved outstanding sales figures in Hungary (37.1%, first place) and in France (37.5%). The Dutch (28.2%) and Romanian (23.2%) markets for perindopril involve significant sales volumes, while in the UK and Polish markets the share is over 10%. The API of perindopril was developed by Servier, France.

Interesting data from the perspective of the analysis is that the market share of captopril—the leading ACE inhibitor therapy, although lagging behind in the clinical ranking—is above 5% in the Hungarian (5.7%), Polish (5.2%) and Romanian (7.3%) markets. (The average price level of captopril is the lowest among the ACE inhibitors.)

Sales figures for the countries presented in Table 11 were subjected to multidimensional scaling. The nine European countries can thus be compared in terms of consumption patterns of 11 different ACE inhibitors. The analysis was undertaken in the same way as before, in SPSS 25.0. In the database, we included an ‘ideal’ variable to represent the country considered to be ideal based on clinical appropriateness (with 100% ramipril sales). The stress index for the fit is 0.0512 (Kruskal's stress formula), and rsq is 0.987,

indicating an extremely close fit. Higher variance can be identified along the first dimension.

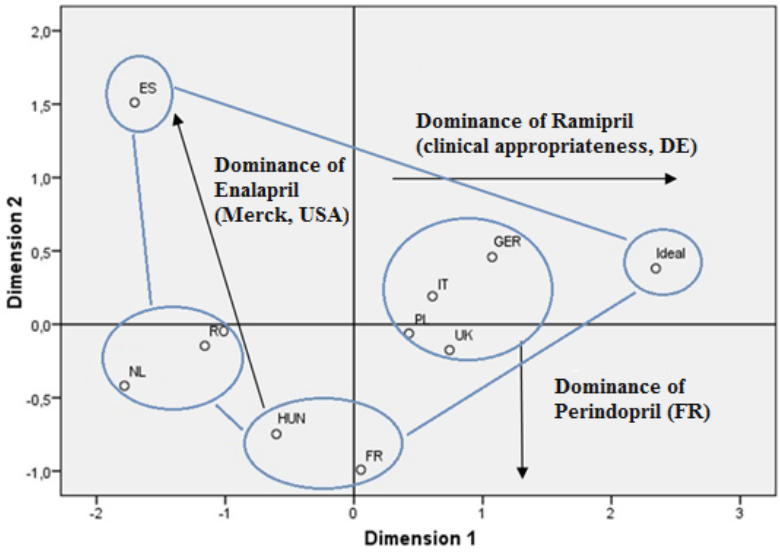


Figure 21 Result of multidimensional scaling based on market data for ACE inhibitor therapies

As shown in the figure, the following groups of countries can be distinguished:

- DE, IT, UK, PL: Countries with the best market performance in terms of ramipril, highly recommended according to its clinical appropriateness. Germany is the country closest to the ideal market in terms of consumption of ACE inhibitors. In addition to ramipril, one (or possibly two) ACE inhibitor(s) showed significant market performance; those from the second category of clinical ranking.
- FR, HU: These countries are dominated by perindopril and ramipril. Since both APIs are the products of a French pharmaceutical manufacturer, these two countries can be characterized as having a strong French influence in terms of ACE inhibitor consumption. (In Hungary, the acquisition of EGIS by Servier and the marketing activities of the Hungarian subsidiary provide an explanation for this phenomenon.) In parallel with perindopril, zofenopril API can be mentioned. The API, developed by Menarini (IT), achieved a sales volume of above 5% only in Italy (8%) and Romania (5.4%) from the countries under study. Both examples suggest a strong country-of-origin effect in the hypertension market. Additionally, a country-of-origin effect may also be a significant factor that influences the market performance of other APIs (e.g., ramipril, lisinopril).
- RO, NL: A dominance of enalapril and perindopril. Interestingly, it is highlighted in the literature that in the Dutch market physician prescribing decisions are not

influenced by price level. However, in the case of ACE inhibitors, it can be concluded that clinical appropriateness is not the main determinant of prescribing in the Dutch pharmaceutical market. The Romanian ACE inhibitor market is the most fragmented among the different markets for APIs in the countries that were compared.

- ES: The Spanish ACE inhibitor market is clearly dominated by enalapril, with ramipril also achieving significant sales.

As to the impact of the price level of ACE inhibitors on market performance, the following conclusions can be drawn. The leading ACE inhibitor, captopril, has the lowest average price level in the studied countries. However, from a clinical point of view, captopril lags behind the first ranked ramipril and the second-ranked API therapies. This may lead to a situation whereby, although it is the cheapest antihypertensive, it underperforms more advanced therapies in terms of market performance. However, in three countries (HU, RO, PL) captopril still accounts for a share of over 5%. This phenomenon is most likely explained by the fact that in these countries there is a highly price-sensitive consumer segment, even for otherwise very cheap ACE inhibitor therapies.

As for sales figures, it can be observed that in the studied countries, therapies that are available at a lower-than-average price level achieve a high market share (after captopril). It is necessary to note that pharmaceutical policy instruments mentioned at the beginning of the literature review also play a major role in shaping price levels, not to mention that patients in the European welfare healthcare systems ‘see’ only a fraction of the real price. Therefore, pharmaceutical policy instruments can be used to influence which therapy is given priority in prescribing decisions. (Assuming a well-functioning healthcare system, therapies with the best risk/return ratio in the long term and at the societal level should be given preference.)

In contrast to the above findings, a significant market share can be seen in a few cases, in spite of the higher-than-average price level. In the German market, the price of ramipril—with a market share of 72.1% and clinically the most appropriate—is above the average ACE price level. The outstanding sales figures of ramipril in the German market can be attributed to several reasons. On the one hand, ramipril is clinically the most appropriate molecule and, on the other, the price level is only marginally, by 2%, higher than the average price level. For sales of ramipril in Germany, the country-of-origin effect may

also play a role during drug detailing. A more striking example, compared to ramipril, is that of perindopril, with high sales figures in several countries. Despite its significantly higher price level compared to the average (+13.8% and +49.3% difference), perindopril achieves sales of between 23% and 37.5% in Romania, Hungary, France, and the Netherlands. Even more striking is the case of zofenopril, which still has an 8% market share in the Italian market despite a 65.5% higher price, and a 5.4% share in the Romanian market despite a 164% higher price. Presumably, the predominance of persuasive marketing power during drug detailing may have led to this market share.

The raw sales data of ACE inhibitors were also examined in European countries. Figures are presented in the table below which indicates APIs in the columns and sales volumes in the rows for nine European countries.

Table 12 Sales volumes of ACE inhibitors in Europe

	BENAZE-PRIL	CAPTO-PRIL	ENALA-PRIL	FOSINO-PRIL	LISINO-PRIL	PERINDO-PRIL	QUINA-PRIL	RAMIPRIL	TRANDOLA-PRIL	ZOFENO-PRIL
IT	10,894	6,885	179,122	12,266	62,268	79,337	13,868	699,434	1,054	93,453
FR	7,910	12,577	49,761	11,851	30,217	341,436	6,256	419,968	21,908	7,282
UK	0	11,356	101,643	1,111	454,336	236,116	5,252	1,166,972	6,249	0
PL	5,362	62,696	144,499	0	70,032	154,554	36,768	654,683	14,597	18,552
ES	2,424	36,428	544,311	4,011	50,117	6,976	6,923	143,541	1,086	0
RO	1,207	41,199	160,858	20,049	36,801	131,364	36,230	104,755	2,983	30,867
NL	86	10,269	111,315	21,455	86,654	102,058	9,532	19,690	0	1,352
DE	10,941	51,673	425,957	6,020	239,912	2,139	8,633	1,928,159	655	0
HU	441	15,564	47,512	5,131	9,071	101,794	3,203	90,527	871	0

This data set was subjected to ALSCAL multidimensional scaling, which created distances from the data based on Euclidean distances. The variables were standardized, and standardized variables and non-standardized variables were implemented. For a better statistical fit, the results of the analysis are presented with non-standardized variables. (The stress index with the original data was 0.043 and rsq was 0.99, while with the standardized variables the stress index was 0.28 and rsq was 0.58.) It is preferred to use non-standardized results for practical interpretation.

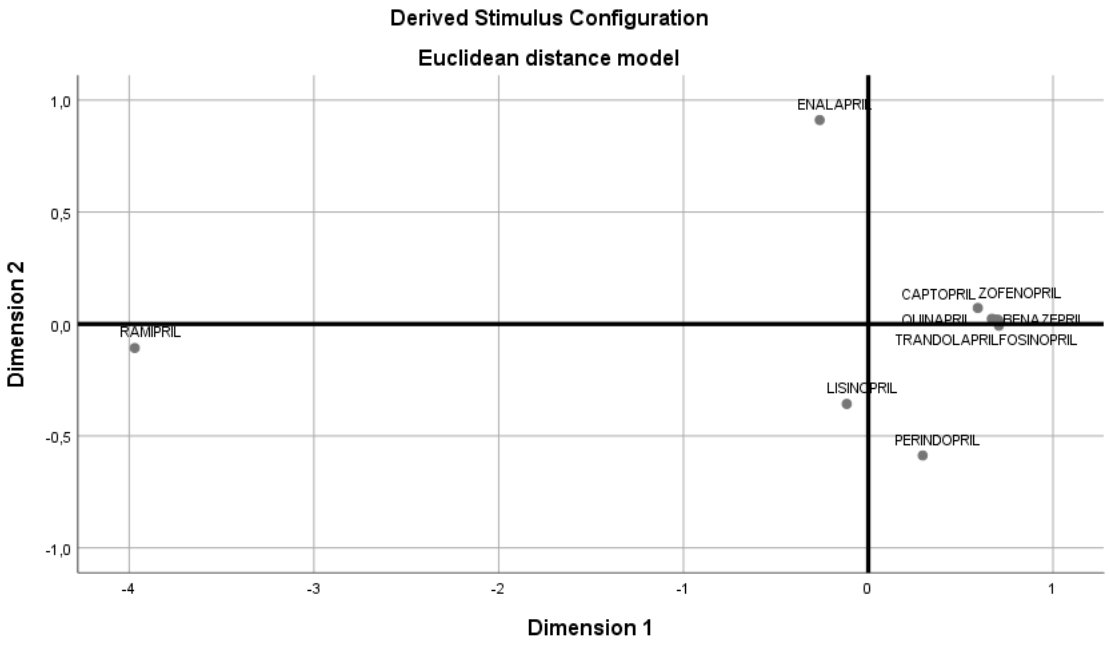
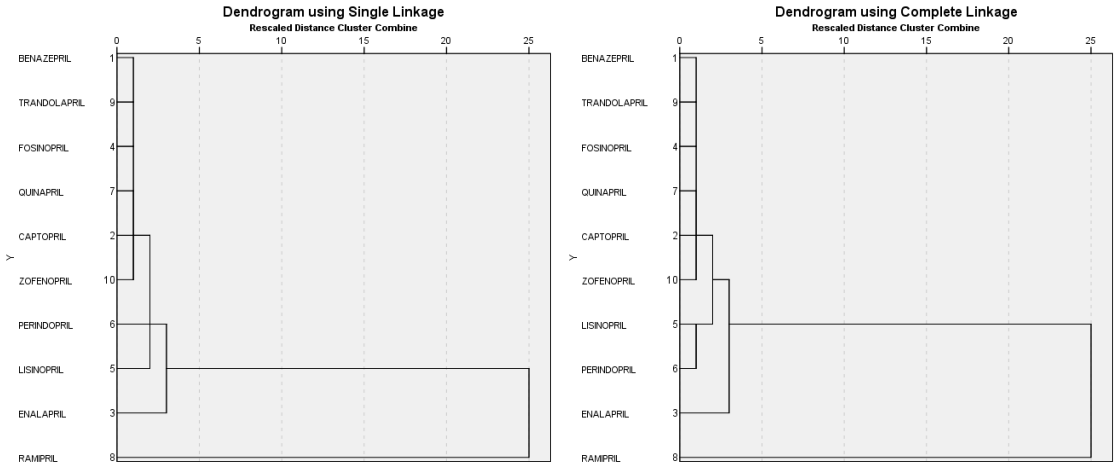


Figure 22 MDS analysis of sales figures of ACE inhibitors

The two-dimensional graph shows how the different APIs can be grouped based on EU sales data. (The interpretation of figures is discussed after the results of the cluster analysis.)

The same dataset was also analysed using cluster analysis, nearest neighbour, furthest neighbour, and Ward's method. The variables were not standardized for the same reason as with multidimensional scaling. The output dendrograms are shown below.



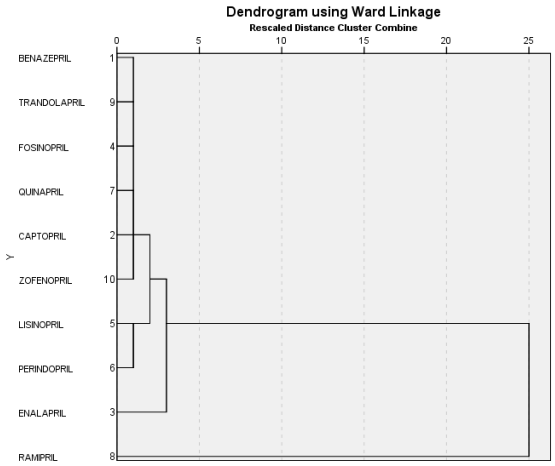


Figure 23 Dendrograms of cluster analysis of ACE inhibitor sales figures (nearest-neighbour, furthest-neighbour, and Ward's method, respectively)

The graphs show that both MDS and cluster analysis produce very similar results. API categories can be clearly defined and distinguished on the basis of the sales figures of different EU countries. The four distinguishing clusters are the following:

- Cluster 1: A class of APIs with very low sales volumes in the studied countries: benazepril, trandolapril, fosinopril, quinapril, captopril and zofenopril. These results are very favourable for patients, considering the fact that APIs with the lowest clinical ranking are contained in this group. The results may be even more encouraging when the price range of APIs is considered. The lowest cost API is the first ‘pril’ in this category: captopril. Despite this lowest cost level, captopril is part of the group of APIs with the least sales.
- Cluster 2: Lisinopril and perindopril. APIs with significant sales figures in some countries, but none of which is a market leader in any country (the only exception is perindopril in Hungary.) Considering the share of sales in different countries, these APIs account for 10–35% of sales.
- Cluster 3: Enalapril. This API is the leading compound in Spain and the Netherlands and achieves ‘similar to second cluster’ sales in PL, RO, HU, DE, and IT.
- Cluster 4: Ramipril. Ramipril is well outside the MDS range and is associated with the largest gap from the other APIs in the dendrograms. The results show that ramipril is the real leader in Europe and associated with the highest sales in Germany, Italy, France, UK and Poland, and significant sales in all other countries except for the Netherlands. The results from the patient perspective suggest very

positive feedback on EU pharmaceutical markets as ramipril seems to be the most suitable compound clinically.

All in all, the methods that are applied are considered appropriate for analysing the market performance of APIs and they help to compare clinical ranking with market potential.

4.2.1.3. Results indicating country-of-origin effects

In the following section, the most striking effects will be analysed both at the API and product level – effects that can be detected on the sales figures and prescription of different APIs in certain countries. Ramipril was developed by Hoescht, a German company, which was acquired by the Sanofi group in 2004. As for ramipril sales data at brand level in Germany, Zentiva, also a member of the Sanofi group, is associated with a 41% market share. The company has a very strong influence in the country. Presumably, their pharmaceutical marketing approach has the greatest impact on prescribing habits.

Within Germany, the market sales of enalapril still have a significant share of 12.7%, and in terms of which manufacturers buy their enalapril products, the answer is Stada, a German pharmaceutical company, with a market share of 52%. In my opinion, this is an excellent example of a preference for a local manufacturer. However, it should also be mentioned that another reason could be the very strong network of sales representatives (identifying the underlying cause of this phenomenon would need further research).

In Italy, the largest share of ramipril sales, 33%, is also generated by Zentiva, a member of the Sanofi group. In Poland, Sanofi is also the market leader for ramipril-containing products, with 27% of market share.

In Poland, a more interesting figure can be found at the brand level. Although enalapril sales are less than 10% (7.3%), 94% of them are made by Polpharma, a local manufacturer. In this case, preference for a local manufacturer can also be observed, presumably with a strong country-of-origin effect, but further research is needed to verify whether this claim is true, as other factors (such as a strong network of sales representatives) may also be responsible for this phenomenon.

Research into the French market reveals that perindopril is the leading API (market share 45.5%). Perindopril was developed by Servier, a French company, and is the market leader in the French perindopril market with a 51% share. Ramipril is the second-best-selling API in France (market share 34%), and there is intense competition between two pharmaceutical companies, Mylan and Servier. There is a small difference between the

two companies in terms of ramipril sales, Mylan achieved 29%, while Servier 24% in 2018. None of the countries reported significant sales of ramipril formulations marketed by Servier except fr France. This suggests that Servier has very strong prescribing power in France, and this is used to market their products. Again, this phenomenon emphasizes the country-of-origin effect and its positive nature.

A strong French influence can also be observed in Hungary, where the market share of perindopril products reached the highest value of 60.9%. Of this, Servier's products account for 55% of the market for perindopril. Similar figures are found for perindopril sales in Romania as well, where Perindopril is the leading API, with Servier's formulations accounting for 57% of the market share in 2018.

According to the IQVIA database, 98% of ACE inhibitors in the UK are labelled as 'lab unknown' in the database, meaning that prescribing physicians do not indicate the brand but only the API when making therapeutic decisions. As a result, no conclusions can be drawn about competition between pharmaceutical manufacturers in this market, nor can conclusions be drawn about the nature of marketing activities.

Research reveals that the strong market sales of enalapril in the Spanish market are probably driven by the support provided by Spanish regulations. Bentley Pharmaceuticals Inc. manufactures its enalapril products in Zaragoza, Spain. Currently, Teva, which acquired Bentley Pharmaceuticals Inc. in 2008, accounts for a 24% share of enalapril sales.

4.2.2. Research into the diffusion of ARBs and ACE inhibitor therapies—market trends in the years 2001, 2016, 2012—2018

4.2.2.1. Comparison of market performance of ACE and ARB therapeutic classes

As a preliminary to the analysis, it is important to clarify the framework of authorization and industrial property rights (IPR) regarding the marketing of these therapies. ACE inhibitors were the first therapies to be approved and introduced from the early 1980s onwards (captopril, enalapril in 1980–1981, lisinopril, perindopril and ramipril in 1987–1988–1989), later followed by other molecules. ACE inhibitors lost their patent exclusivity mainly in the 1990s and early 2000s, although manufacturers tried to extend patent protection by infringing legislation (see the case of perindopril before). ARB entered the market first in 1995 with losartan (with valsartan in 1996, and with candesartan in 1997). Losartan and candesartan became generics in the early 2010s. By

2016, all major ARBs had become generic. Innovative and generic market entries determine market patterns in a very complex way.

The approach described in the methodology chapter was used to analyse the macro trends in market performance. The analysis of the aggregate sales of ARBs and ACE inhibitors was repeated for the data available from 2001, the earliest year in the database, and from 2009, the middle of the period, so that the analysis reveals a 15-year trend. As an means of providing an outlook on sales figures of ACE therapies, data for 2018 are also presented.

Looking at the data from 2001 (Table 13), all markets were dominated by ACE inhibitors. Two groups can be identified: the first group includes Hungary, Poland, and Romania, with virtually no ARB sales; the second group includes Western countries, with ARB sales volumes ranging from 14% to 37%. Comparing relative prices, in the first group of countries ARBs were much more expensive than ACEIs (four to eight times more), while in the Western group ARBs were also more expensive on average, but to a lesser extent. In 2001, the overall ARB preference index was below '1' compared to the result in 2009, even though ARBs accounted for more than 40% of sales in France and Spain.

Table 13 Market characteristics of ARBs and ACE inhibitors based on DDD-adjusted volumes considering combination and single-ingredient drugs, 2001

	ARB price level (EUR/DDD)	ACEI price level (EUR/DDD)	ARB volume (DDD, %)	ARB revenue (EUR, %)	ACEI volume (DDD, %)	ACEI revenue (EUR, %)	ARB: ACEI price level ratio	ARB: ACEI volume ratio	ARB: ACEI revenue ratio	ARB preference index
FR	0.59	0.43	37.34	**44.85**	62.66	55.15	1.36	0.60	0.81	0.48
DE	0.57	0.27	21.61	**36.81**	78.39	63.19	2.11	0.28	0.58	0.16
HU	0.52	0.12	1.03	4.31	**98.97**	95.69	**4.32**	0.01	0.05	0.00
IT	0.53	0.38	24.75	**31.56**	75.25	68.44	1.40	0.33	0.46	0.15
PL	0.56	0.09	0.19	1.16	**99.81**	98.84	**6.01**	0.00	0.01	0.00
RO	0.82	0.10	0.09	0.69	**99.91**	99.31	**8.16**	0.00	0.01	0.00
ES	0.46	0.24	29.99	**45.47**	70.01	54.53	1.95	0.43	0.83	0.36
UK	0.81	0.36	14.23	**27.11**	85.77	72.89	2.24	0.17	0.37	0.06

Abbreviations: FR–France, DE–Germany, HU–Hungary, IT–Italy, NL–The Netherlands, PL–Poland, RO–Romania, ES–Spain, UK–United Kingdom

An analysis of the data from 2009 shows that the relative prices of ARBs were strikingly higher in the studied countries (Table 14). For example, the difference in cost between the two classes of drugs was ten times higher in Germany and in the UK. Presumably due to this fact, the volume share of ARBs exceeded that of ACE inhibitors in only two countries (France and Spain). In Germany, Hungary, Poland, Romania, and the United Kingdom, ACE inhibitors accounted for 70–90% of DDD-adjusted sales volume, and in

the three Central and Eastern European countries, this class of drugs also accounted for the majority of manufacturer revenue. Except for in the UK, the preference index was above '1' in all Western European countries, with Spain, the Netherlands and France having the highest values. ARBs were more expensive in 2009 than in 2016, and the share of manufacturer revenue was also higher in most Western European countries with similar volumes.

Table 14 Market characteristics of ARBs and ACE inhibitors based on DDD-adjusted volumes considering combination and single-ingredient drugs, 2009

	ARB price level (EUR/DDD)	ACEI price level (EUR/DDD)	ARB volume (DDD, %)	ARB revenue (EUR, %)	ACEI volume (DDD, %)	ACEI revenue (EUR, %)	ARB: ACEI price level ratio	ARB: ACEI volume ratio	ARB: ACEI revenue ratio	ARB preference index
FR	0.54	0.29	**54.79**	**68.92**	45.21	31.08	1.83	1.21	2.22	**2.69**
DE	0.54	0.05	26.35	**79.20**	**73.65**	20.80	**10.64**	0.36	3.81	1.36
HU	0.36	0.10	14.32	37.93	**85.68**	**62.07**	3.66	0.17	0.61	*0.10*
IT	0.45	0.16	41.44	**65.94**	58.56	34.06	2.74	0.71	1.94	1.37
NL	0.51	0.07	43.55	**85.52**	56.45	14.48	**7.66**	0.77	5.91	**4.56**
PL	0.17	0.06	11.30	26.86	**88.70**	**73.14**	2.88	0.13	0.37	*0.05*
RO	0.28	0.08	13.35	34.06	**86.65**	**65.94**	3.35	0.15	0.52	*0.08*
ES	0.48	0.10	**55.30**	**85.05**	44.70	14.95	4.60	1.24	5.69	**7.04**
UK	0.37	0.04	22.32	**74.76**	**77.68**	25.24	**10.31**	0.29	2.96	0.85

Abbreviations: FR–France, DE–Germany, HU–Hungary, IT–Italy, NL–The Netherlands, PL–Poland, RO–Romania, ES–Spain, UK–United Kingdom

In general, the volume share of ACE inhibitors continued to be greater than that of ARBs—based on DDD-adjusted sales data in 2016—so the upward trend in ARB sales observed between 2001 and 2009 stopped increasing (Table 15). France, Spain, the Netherlands, and Italy accounted for the largest ARB shares in DDD-adjusted volumes, with the first two countries exceeding 50%, while Italy and the Netherlands had a market share of more than 40%. In contrast, ACE inhibitors accounted for more than 70% of DDD-adjusted sales volumes in Poland, the UK, and Romania. In Poland and Romania, ACE inhibitors also accounted for a large share of manufacturer revenue, similarly to in the third Central and Eastern European country, Hungary. In other countries, ARBs accounted for a larger share of manufacturer revenue. In Spain and Germany, ARBs accounted for more than three-quarters of revenue associated with the whole drug class. The difference in average price levels between ACE inhibitors and ARBs—a possible cause and implication of these effects—was also the greatest in these two countries, as was the ARB preference index. The ARB preference index, which reflects the relative sales and estimated price levels of the two sub-classes, was 1.95 and 5.83 in the German and Spanish markets respectively, indicating significant ARB sales. A value of about '1'

for France, Italy and the Netherlands indicates balanced market conditions, while a value of between 0.1 and 0.3 for Poland, Hungary and the UK confirms the continued dominance of ACE inhibitors on the market. In general, ACE inhibitors were cheaper than ARBs in all nine countries, although the price level shows that the gap clearly narrowed between 2009 and 2016.

Table 15 Market characteristics of ARBs and ACE inhibitors considering combination and single-ingredient drugs, 2016

	ARB price level (EUR/DDD)	ACEI price level (EUR/DDD)	ARB volume (DDD, %)	ARB revenue (EUR, %)	ACEI volume (DDD, %)	ACEI revenue (EUR, %)	ARB: ACEI price level ratio	ARB: ACEI volume ratio	ARB: ACEI revenue ratio	ARB preference index
FR	0.20	0.15	**50.63**	57.04	49.37	42.96	1.29	1.03	1.33	1.36
DE	0.19	0.04	37.56	**76.44**	62.44	23.56	**5.39**	0.60	3.24	**1.95**
HU	0.10	0.09	27.07	29.48	**72.93**	**70.52**	1.13	0.37	0.42	*0.16*
IT	0.22	0.12	**43.85**	58.65	56.15	41.35	1.82	0.78	1.42	1.11
NL	0.07	0.04	**45.42**	59.88	54.58	40.12	1.79	0.83	1.49	1.24
PL	0.11	0.05	25.04	40.69	**74.96**	59.31	2.05	0.33	0.69	0.23
RO	0.12	0.07	28.44	40.61	**71.56**	59.39	1.72	0.40	0.68	0.27
ES	0.31	0.06	**51.66**	**84.52**	48.34	15.48	**5.11**	1.07	5.46	**5.83**
UK	0.10	0.03	22.71	52.12	**77.29**	47.88	**3.70**	0.29	1.09	*0.32*

Abbreviations: FR–France, DE–Germany, HU–Hungary, IT–Italy, NL–The Netherlands, PL–Poland, RO–Romania, ES–Spain, UK–United Kingdom

Comparing the multidimensional scaling results (Figure 24), a clear dominance of ACEI therapies is demonstrated in 2001 (countries close to '0' in dimension 2). It should be noted that, at that time, ARB therapies had only been present in the different markets for a few years. Until 2009, the increasing trend to ARB use can be observed, which can be explained by their steadily growing acceptance and by the maturing of innovative ARB brands in 2009. ARB sales increased despite the significant price index increase between ACEIs and ARBs (ARBs are 1.83–10.64 times more expensive than ACE therapies in different countries). One of the reasons for the price index increase is that ACEI brands becoming generic lowered their price, while ARB APIs maintained their innovative status and monopolistic position. Accordingly, competition in the ACEI markets existed at the brand level and in the ARB markets at the API level. By 2016, the prices of both ARB and ACE therapies fell significantly, and the price index scissors between the two classes closed to a range of 1.13–5.11, still in favour of ARBs. Interestingly, although the price level of ARBs declined and their relative price to ACEIs also declined over the period under review, the volume dominance of ARB sales did not follow this trend: the volume ratio between ACEIs and ARBs remained almost identical in 2009 and 2016. Therefore, the multidimensional scaling shows a closing pattern.

Interpretation of the data for the countries shows that although the relative position of the Western European countries changed, the position of the three Eastern European countries—reflecting the lower level of ARBs consumption—remains relatively similar and differs strongly from that of the Western countries in the overall time series. In 2009, prior to the introduction of generic ARBs, the German and the UK markets formed one group characterized by less frequent use of ARBs. Also, distinguishable (in 2009) is the Italian and French country pair, and the Dutch and Spanish country pair. As regards the data in the tables above, these pairs were associated with very similar relative prices for ARBs and for the ACEI class, and the pairs also had very similar shares of the ARB market. The stress index fits the data well for each year.

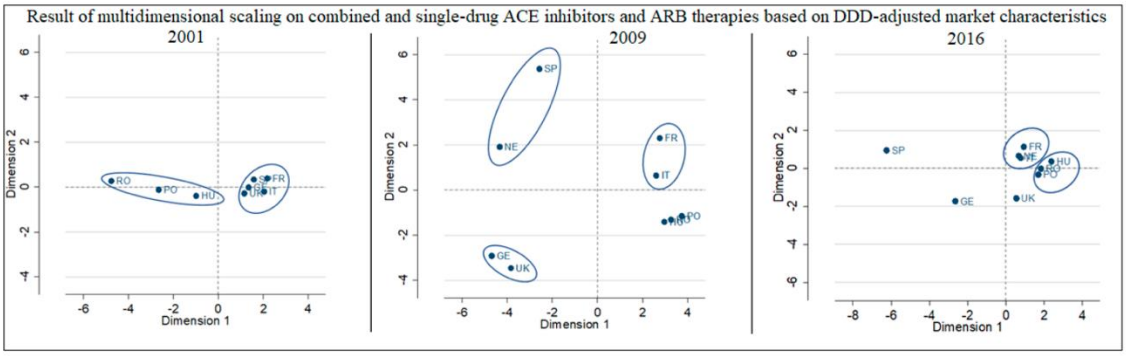


Figure 24 Results of multidimensional scaling for combination and single-ingredient ACE inhibitors and ARBs based on DDD-corrected market characteristics in years 2001, 2009 and 2016: 2001: r = 1.0000, ρ = 0.9984, Kruskal stress index: 0.0056; 2009: r = 1.0000, ρ = 0.9999, Kruskal stress index: 0.0045; 2016: r = 1.0000, ρ = 0.9990, Kruskal stress index: 0.0048.

Trends can be better estimated, and countries can be more sharply differentiated by plotting the ARB preference index and price level from time to time, such as from year to year (Figure 25). In the UK, Hungary, Poland, and Romania, the preference index has remained low over the period under investigation. In contrast, despite high prices, ARBs are responsible for a significant share of the market in the other five countries, leading to a peak in the preference index curve around 2010, before ARB prices started to fall.

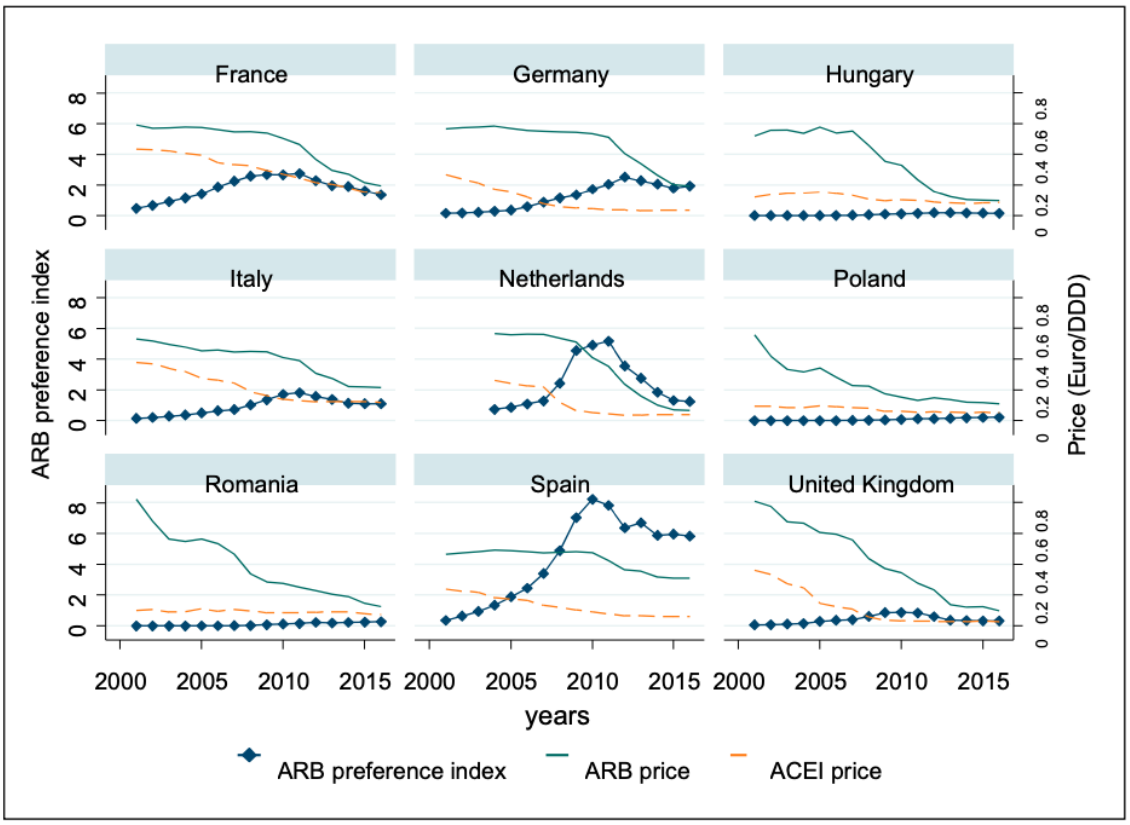


Figure 25 ARB preference index and average prices for ARBs and ACEIs

As generic prices fell dramatically, the market share of ARBs increased in the three Central Eastern European countries and in Germany; however, in France, Spain, Italy, and the Netherlands, the increase in the volume share of ARBs stopped around 2010 when prices started to fall. It should be stressed that the average price level of ARBs was higher than that of ACE inhibitors in all countries, but the relative price difference between ARBs and ACE inhibitors decreased in all countries. In Hungary and the Netherlands, the price of ARBs was close to that of ACE inhibitors in the last years, while in Romania and Poland the price levels were almost identical. The largest difference in price levels remained in the Spanish market.

4.2.2.2. Change in preferences for ACE inhibitors

In the following analysis, the market trends to genericization in its late phase (2001–2016) and the following period (2012–2018) are described in detail. At the end of the analysis, the most recent data for 2021 are also examined. Countries account for different weights in terms of their share of the total market, so it is worth reviewing the changes in aggregate volume data. Data between 2012 and 2018 are shown in Figure 26.

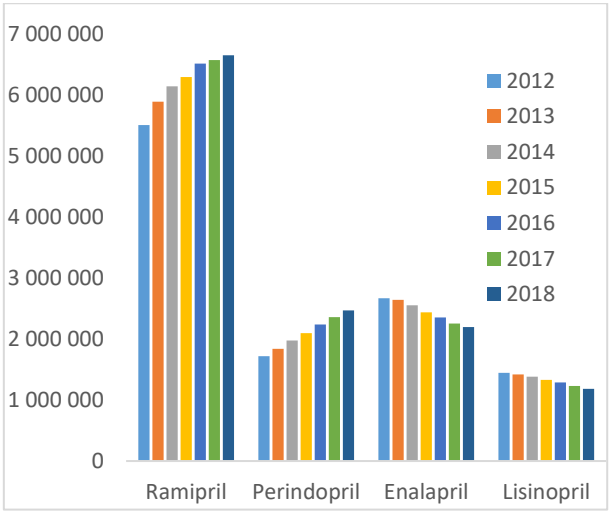


Figure 26 Annual sales volumes of the four ACE inhibitors in nine countries, 2012–2018

The figure illustrates the clear lead of ramipril in the aggregate sales data for the nine countries and shows that, albeit at a slower pace, the share of sales increased over the whole period. There was also an increase in sales of perindopril, but sales of enalapril and lisinopril decreased steadily.

A comparison of annual sales of APIs by country reveals the following trends (see Figure 27).

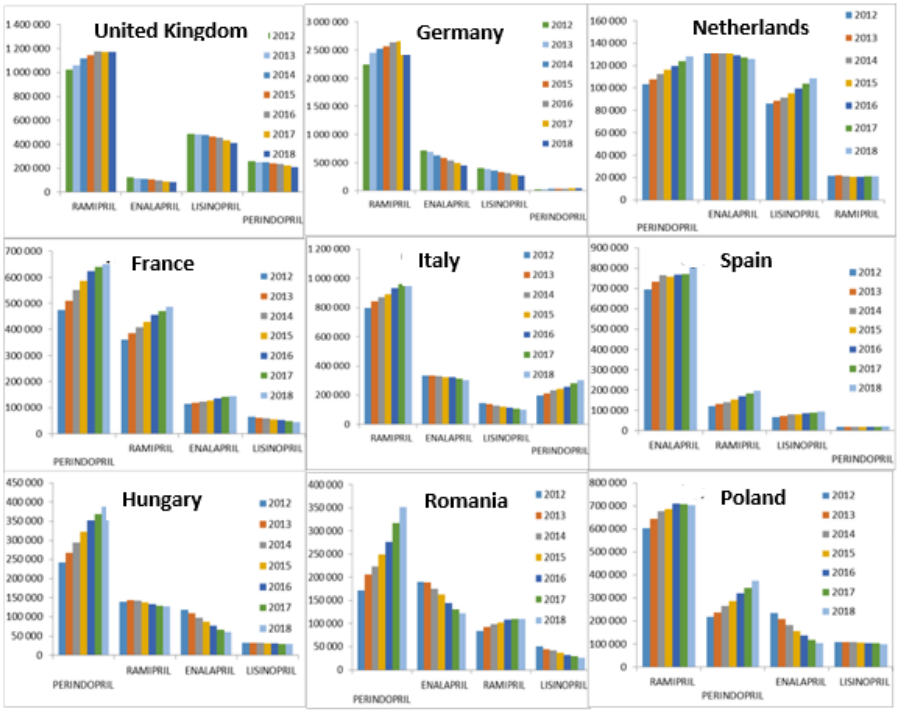


Figure 27 Annual sales volumes of the four main ACE inhibitors, 2012–2018 (Source: author's construction based on IQVIA database)

Since 2012, there has been no change in the order of APIs associated with the largest market share (%) in the countries. In the nine countries, the total number of tablets and capsules sold increased for ramipril and perindopril, while the market performance of enalapril and lisinopril decreased. As for ramipril sales, all other countries have seen an increase by an average of 20% in 2018 compared to 2012, except for Hungary, where sales decreased. In the UK and Germany, the sales of enalapril, lisinopril and perindopril declined over the six years, while ramipril sales increased – presumably specialists increased their use of ramipril at the expense of the other three.

In Italy, although there was a significant difference between ramipril and perindopril sales in favour of ramipril over the six years, an increase in perindopril sales can be identified. An almost identical trend occurred in Poland as well. This trend also corresponds to perindopril sales in the nine countries involved in the analysis.

In France, alongside perindopril sales (37% increase in 2018 compared to 2012), ramipril sales also increased almost at the same rate (34% increase). In the six years under review, perindopril sales increased by 60% in Hungary and doubled to 100% in Romania. These are outstanding figures compared to other countries.

Lisinopril has a significant market share in the UK and the Netherlands; that is, a market share of more than 10%. While its market share in the Netherlands increased by 25% since 2012, it has decreased by 15% in the UK over the same period. It is also interesting to note that although in Spain lisinopril had not achieved a market share of 10%, its market sales increased rapidly by 40% in the six years.

My research aims to investigate the impact of clinical evidence on market performance. Accordingly, to obtain an even deeper understanding of the trends in the change of market share, the market performance of the three Central and Eastern European countries, Germany, France, and the UK is compared for ACE therapies over the entire genericization period of 2001–2016.

In general, sales volumes of ACE inhibitors increased in the selected European countries over the period under review. The market shares of DDD-adjusted volumes show (Figure 28) that diffusion of the dominant drugs was the key market feature during the period. By 2016, except for in Hungary and Romania, where perindopril was the most popular drug, ramipril became the market-leading therapy. In the UK, ramipril has accounted for the largest market share since the mid-2000s. However, in Germany and Poland, it replaced the former market leader enalapril within a few years after 2007–2008. In France, sales

volumes of perindopril have come close to those of ramipril, and since about 2008 the market shares of the two APIs have become stable. Similarly, the market share of perindopril in Hungary and Romania has been increasing since 2008. The market share of enalapril was substantial in Poland, Hungary, Germany, and Romania in the early 2000s, but subsequently declined significantly in almost all countries. Captopril, the first ACEI, also had a large market share in Romania, and Germany in the early 2000s, but its importance declined towards the end of the period. Lisinopril obtained a larger market share mainly in France, Germany, and the United Kingdom, but its relative market share declined except for in the United Kingdom. Surprisingly, unlike in other countries, the relative sales of different APIs in France and Poland did not changed much since 2011–2012, except for a slow decline in sales of lisinopril and enalapril in favour of perindopril and ramipril. Interestingly, the growth rate of ramipril's market share slowed down temporarily for three to four years after 2004, when perindopril's share increased.

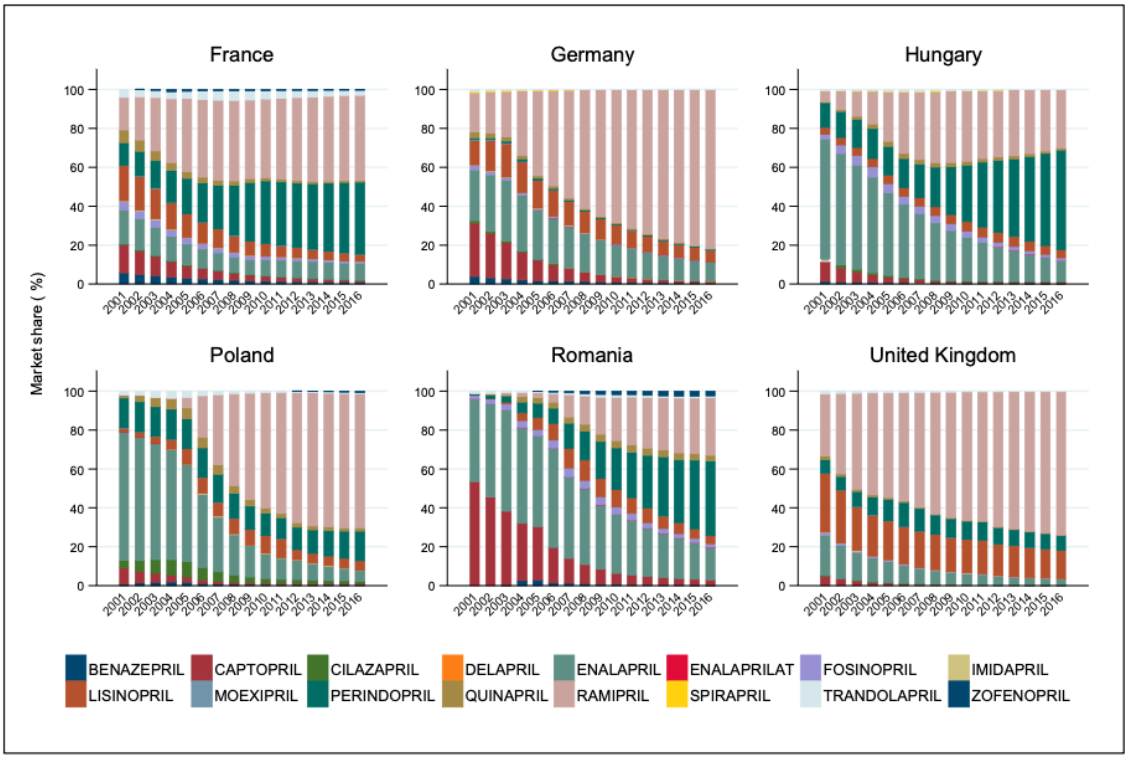


Figure 28 Volume share of ACE inhibitors (combination drugs and mono formulations) in six European countries, 2001–2016

Apart from the products discussed above, other APIs are of minor importance, but some country-specific features are worth mentioning. In the French and Romanian markets, trandolapril had a significant market share in the early 2000s, while zofenopril only in Romania, France, and Poland and only with a small market share. Cilazapril had a

significant market share mainly in Poland, quinapril in Poland, Romania, and France and fosinopril in Hungary, Romania, and France.

The market performance of APIs is determined by several factors, as described in the literature review. To paint a clear picture, the price level, number of brands, and DDD-adjusted volume share of the five most important drug therapies—captopril, enalapril, lisinopril, perindopril and ramipril—in terms of market share are plotted in Figure 29. The graph illustrates that prices of the most used ACE inhibitors decreased between 2001 and 2016. It can also be confirmed that the increase in the number of brands inversely affected the price level: ramipril decreased significantly in all markets, but perindopril less so (in Germany, for example, there was almost no change). The price of enalapril remained stable in France, similarly to zofenopril in France and Romania, and lisinopril in Hungary. As for prices in general, prices of APIs with lower sales volumes were usually higher. Finally, the price of ramipril was one of the lowest on the market in the last few years of the period under review.

The overall number of ACE inhibitor brands continued to increase around 2010, while after that it stagnated or even declined in most countries. In Germany, the number of brands reached a peak slightly earlier, in around 2007, but then declined more rapidly than in other countries due to a sharp decline in the number of captopril brands. The number of perindopril brands surged between 2008 and 2010 (except for in Germany), and after that APIs with a larger market share—captopril, lisinopril, perindopril, ramipril, enalapril, trandolapril, quinapril and fosinopril—became part of a multi-player market. This coincided with a period during which the number of ARB brands started to increase. By contrast, the price of single-ingredient ACE inhibitors—apart from perindopril—started to fall in most countries in around 2005, with a parallel increase in the number of brands, and after a few years combination drugs also entered the competitive arena.

In most countries, both the price and the market share of captopril, enalapril and lisinopril steadily decreased over the period, while the number of enalapril and captopril brands started to increase in the early 2000s, then more or less stabilized and after that started to decrease. In contrast to in other countries, the price of captopril increased slowly in Hungary until 2010, while in the UK prices increased between 2013 and 2015 (the generic competition paradox).

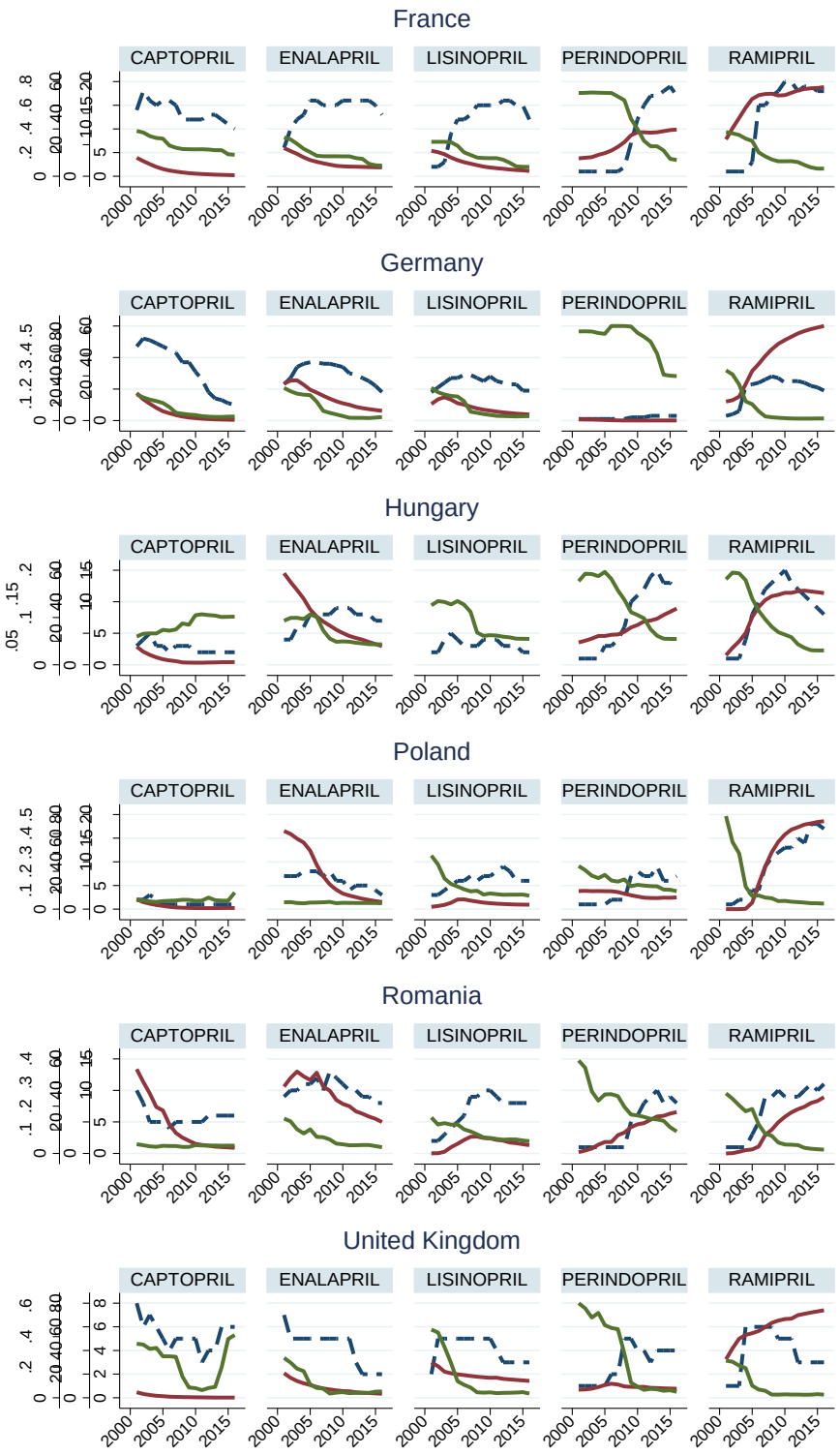


Figure 29 Changes in sales, price, and number of brands of single-ingredient ACE inhibitors (top five APIs with the largest market share) Blue dotted line (- - -): number of brands; red straight line (-): DDD-corrected volume; green straight line (-): price of DDD.

One feature of lisinopril should be highlighted: the Polish and Romanian markets show a small market share for the latter following a price cut in 2005. In France, the price decrease and the sharp increase in the number of perindopril and ramipril brands indicates

the entry of generics around 2005 and 2008. Prior to this, the market share of these two APIs increased but remained basically stable for the rest of the period. In the German, Polish and UK markets, the volume share of perindopril did not change significantly despite the price drop, but the market share of ramipril increased rapidly, with falling prices and growth in the number of brands in these three markets and in Hungary and Romania. However, the market share of perindopril increased steadily in Hungary and Romania. Here, despite rapid growth in the number of brands, prices decreased comparatively slower.

Market fragmentation or concentration is indicated by the Herfindahl-Hirschman Index (HHI). Figure 30 illustrates the annual HHI scores of the ACE inhibitor markets in six countries. Both DDD-adjusted volume and revenue-based calculation are included in the analysis, as well as the raw calculation without DDD adjustment. In the case of Western countries, the HHI for ramipril and perindopril is steadily increasing as the market position of ramipril and perindopril strengthens.

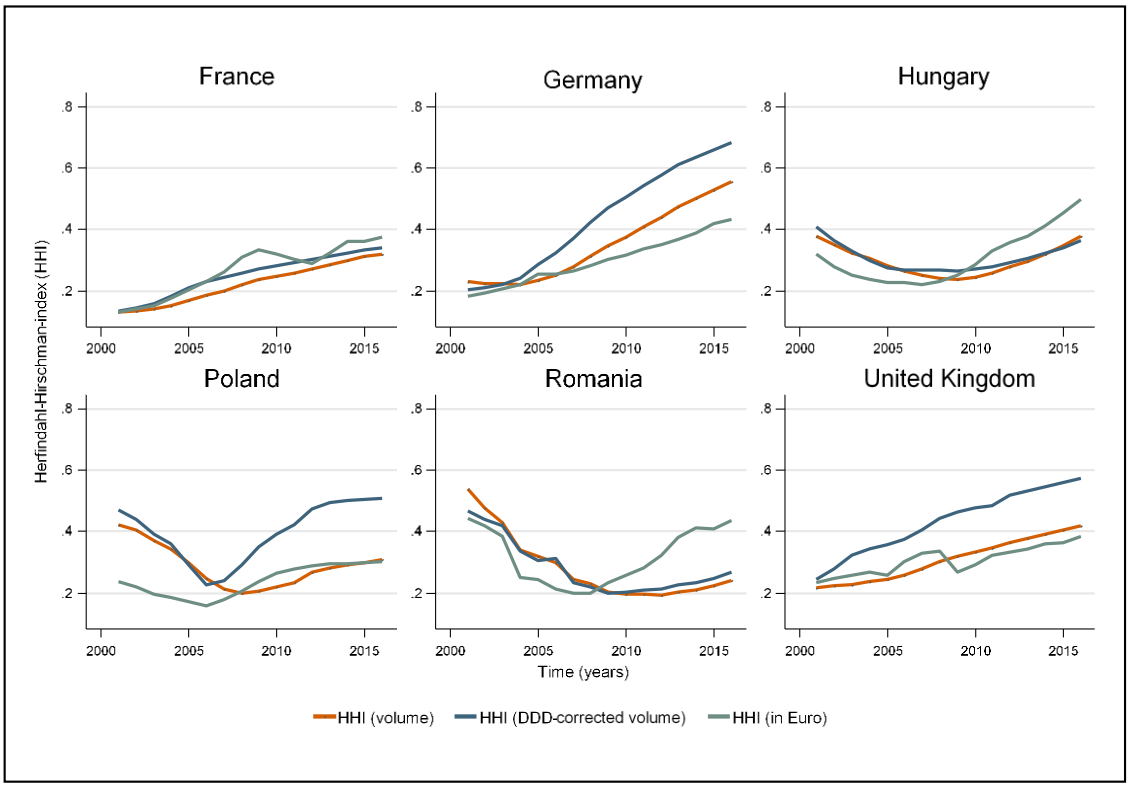


Figure 30 Market concentration of ACE inhibitors in six European countries, 2001–2016

In the CEE region, the relatively concentrated markets become more fragmented until the middle of the period, causing HHI to decrease, and then to grow again as ramipril and perindopril became dominant. In Germany, the UK, and Poland, the HHI values

calculated using raw and DDD-adjusted volume data become increasingly distant. A partial explanation suggests that ramipril is used in clinical practice at higher doses than DDD (as opposed to perindopril). In line with the earlier presented figures, market concentration in Poland stopped rising after 2012.

The focus of my doctoral research is the process of genericization; therefore, a detailed investigation was carried out into ACE inhibitors for the period between 2001 and 2018. However, as an outlook, a cross-sectional analysis of volume shares is also provided for 2021. Figures show that ramipril has maintained its leading position in the German, UK, Italian and Polish markets. Perindopril has become the undisputed market leader in Hungary, Romania, France and, albeit with only a slight lead, in the Netherlands. Enalapril remains the market leader in Spain and is sold in significant volumes on the Dutch market. Lisinopril has significant sales volumes in the UK and the Netherlands. Zofenopril significantly increased its market share on the Italian market, reinforcing the emergence of the country-of-origin effect.

Table 16 Market share of ACE inhibitors by volume at API level for all studied countries, 2021

API	UK	DE	NL	FR	IT	ES	HU	PL	RO
ramipril	**66.0**	**79.7**	4.5	**35.2**	**49.8**	**18.0**	**17.8**	**46.6**	**13.5**
enalapril	3.8	**10.4**	**29.4**	10.0	**13.0**	**66.5**	6.7	4.9	**11.8**
fosinopril	0.0	0.1	4.3	0.6	0.8	0.3	0.9	0.0	1.4
lisinopril	**20.0**	6.4	**29.7**	2.5	3.9	8.3	4.3	6.4	2.4
perindopril	9.6	2.1	**31.7**	**47.2**	**18.6**	1.9	**67.3**	**31.0**	**61.0**
zofenopril	0.0	0.0	0.2	0.4	**10.3**	0.0	0.0	3.1	3.1
captopril	0.3	0.8	0.1	0.8	0.4	2.0	2.5	4.7	5.1
trandolapril	0.2	0.0	0.0	2.5	0.0	0.2	0.1	0.4	0.5
benazepril	0.0	0.3	0.0	0.6	0.7	0.1	0.1	0.2	0.0
quinapril	0.0	0.2	0.0	0.3	1.0	0.5	0.3	1.5	1.1
moexipril	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: FR–France, DE–Germany, HU–Hungary, IT–Italy, NL–The Netherlands, PL–Poland, RO–Romania, ES–Spain, UK–United Kingdom

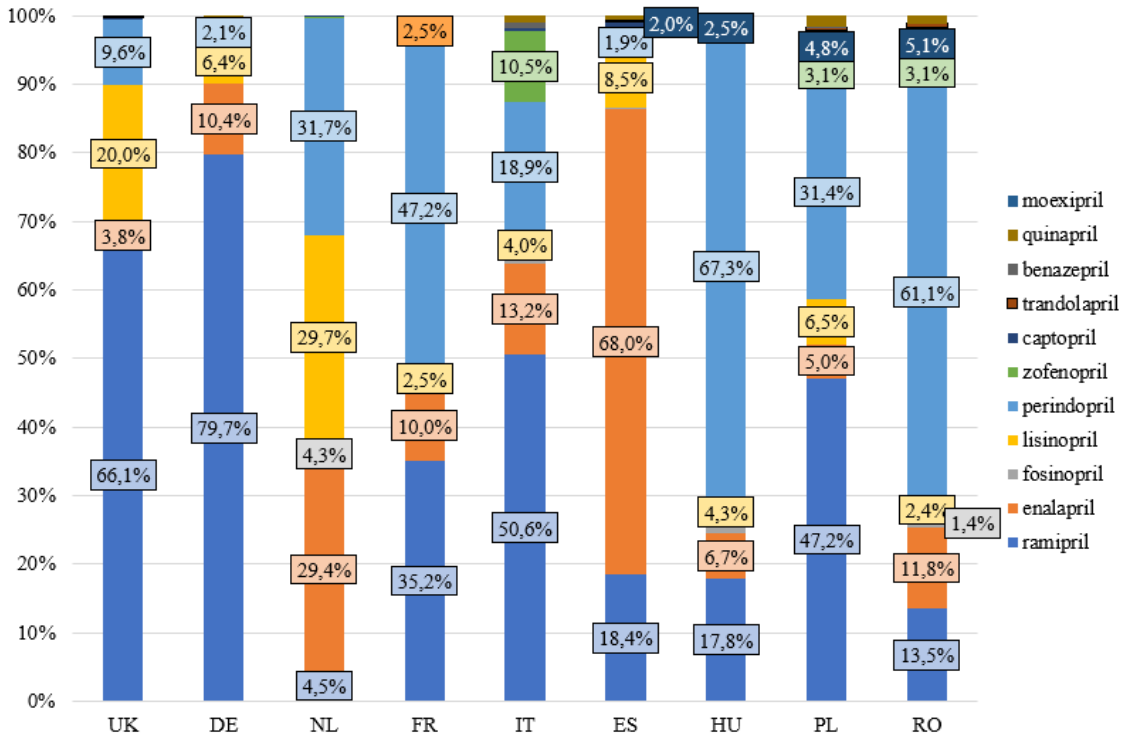


Figure 31 Market share of ACE inhibitors by volume at API level for all studied countries, 2021

4.2.3. ACE and ARB markets in Hungary in 2021

To obtain a deeper understanding of the trends after genericization, marketing research was carried out in the Hungarian market, and research results are analysed in detail in this chapter. However, to be able to investigate the impact of influencing factors on prescribing behaviour, from a methodological point of view it is necessary to compare the primary research results with aggregate market data. For this reason, the market performance of ACE and ARB therapies is analysed in the Hungarian market separately for the year 2021, when the survey was conducted.

The share of antihypertensive drugs prescribed in 2021 will continue to lean towards ACE inhibitors, with nearly three-quarters (73.86%) of patients receiving ACE inhibitors and only a quarter (26.14%) of them receiving ARB inhibitors. As for ACE inhibitor therapies, perindopril has consistently and significantly increased in terms of sales, with its share reaching 67.3%. Ramipril has a market share of about 17.5%, enalapril and lisinopril about 5%, and captopril's share decreased to 2.5%.

ARB inhibitors do not show the same level of market concentration as ACE inhibitors. In our case, telmisartan is the market leader (35.49%), followed closely by valsartan

(31.90%). Losartan (19.61%) and irbesartan (10.89%) occupy the third and the fourth place.

The market concentration of ACE inhibitors is even more pronounced when the share of each API is investigated according to units sold, with perindopril accounting for almost half of all the prescriptions (49.73%), followed by ramipril (13.16%) and the two most popular ARB inhibitors (telmisartan: 9.28 %; valsartan: 8.34%). (See Table 17)

Table 17 Market share of ACE and ARB inhibitors in Hungary in 2021

API	Counting units	Market share	
		By class	Total
benazepril	353,570	0.05%	0.04%
captopril	16,515,330	2.52%	1.86%
cilazapril	278,852	0.04%	0.03%
enalapril	43,608,050	6.66%	4.92%
fosinopril	5,616,466	0.86%	0.63%
lisinopril	28,159,316	4.30%	3.18%
perindopril	440,602,860	**67.33%**	**49.73%**
quinapril	2,047,590	0.31%	0.23%
ramipril	116,575,380	**17.81%**	**13.16%**
trandolapril	626,944	0.10%	0.07%
Total ACE inhibitors	**654,384,358**	**73.86%**	**73.86%**
andesartan cilexetil	3,818,190	1.65%	0.43%
eprosartan	14,560	0.01%	0.00%
irbesartan	25,212,556	**10.89%**	2.85%
losartan	45,394,728	**19.61%**	5.12%
olmesartan medoxomil	1,075,144	0.46%	0.12%
telmisartan	82,170,272	**35.49%**	9.28%
valsartan	73,856,192	**31.90%**	8.34%
Total ARB inhibitors	**231,541,642**	**26.14%**	**26.14%**
Total	**885,926,000**	**100.00%**	100.00%

4.2.4. Results of the primary market research

Marketing research was carried out to investigate the extent of influencing factors on prescribing decisions. A survey was conducted using a standard questionnaire. The survey was implemented online among physicians and sales representatives. The respondents were sales representatives of one pharmaceutical company and physicians associated with the company, so our sample is not representative of physicians and sales representatives in Hungary, thus the results cannot be other than exploratory.

The questionnaire was partly based on a validated questionnaire from the literature that had been used for research with similar aims, and partly on my qualitative research. Some

changes were made to the questionnaire: a few questions were added based on the results of the qualitative research, and some were left out (the irrelevant ones in relation to the domestic market).

The aim of research by Nutescu et al. (2005) was to identify the most important determinants of physicians' decisions to prescribe a drug within a therapeutic category. A questionnaire survey was implemented among hospital physicians and clinical pharmacists. The factors affecting drug prescribing behaviour were compiled in line with the factors from a model published in the literature (Denig et al., 1988), and these were classified into three categories: 'drug-related', 'direct', and 'indirect'. The scales used in the Denig model were modified by Nutescu et al. based on their expert interviews and validated accordingly. Each item was rated on a six-point Likert scale, with zero indicating 'no effect' and 5 indicating 'most significant effect'.

Since the aim of my research is very similar to that of the research conducted by Nutescu et al. (2005), their scale was applied in my questionnaire. All the items were included that were relevant in the studied therapeutic area and in Hungarian healthcare, then statements were added that emerged in the qualitative research and proved to be relevant for the primary research. The questionnaire consisted of 33 influencing factors affecting drug choice decisions, of which 9 were of 'drug-related', 8 'direct' and 16 'indirect'.

The investigated area is the treatment of hypertension, including drug choice of ACE inhibitors and ARB therapeutic class. The survey was conducted online, with the participation of physicians and sales representatives (154 physicians and 106 sales representatives). The main reason for choosing two target groups is that presumably factors are perceived differently by prescribing physicians and sales representatives, the latter representing the marketing efforts of the company. This allows for a comparison that has not been made in the literature before.

At first, the responses of sales representatives and physicians regarding 33 statements on prescribing behaviour were compared to identify if there were significant differences between the responses of the two groups. For most statements, significant differences were detected between the responses. There was only one case where the average of physicians' responses was higher than that of the sales representatives': Statement 3, about clinical efficacy. In all other cases, the significant differences meant a higher average for sales representatives. Differences were revealed for the following questions:

- 10. Availability of written professional information about the therapy, professional content
- 11. Information received from pharmaceutical companies during drug detailing
- 13. Opinions and recommendations from peers
- 14. Information about hospital prescribing practices
- 15. Drug samples provided by pharmaceutical companies
- 16. Research support provided by pharmaceutical companies
- 18. Education, training programmes sponsored by pharmaceutical companies
- 19. Pharmaceutical industry presence at professional events
- 20. Advertisements in professional journals (paper and online)
- 21. Quality of materials from sales representatives
- 22. Small gifts from pharmaceutical companies (pens, etc.)
- 24. Drugs were developed in Hungary
- 26. Visual appearance and packaging of drugs
- 27. Slogans of pharmaceutical companies, brand associations
- 28. Form of financing for a particular therapy
- 29. Recommendations from recognized physicians, opinion leaders
- 30. Good relationship between physicians and sales representatives
- 31. Expertise of sales representatives
- 32. Stability of the pharmaceutical company (history)
- 33. Drugs are produced in Hungary

On average, physicians consider professional data and facts about drugs to be the most significant factor, and regarding information, more direct types of information—received either from studies or from prescribing guidelines or from sales representatives—is also regarded as very important. Information in the indirect category—obtained through the marketing activities of pharmaceutical companies, such as educational material or events provided by companies—is rated below average and appears to be less important. Among the marketing efforts of pharmaceutical companies, drug detailing is strongly recognized by physicians, and both the expertise of sales representatives and their relationship with physicians are rated as average. See Table 18/a–c.

Table 18a Comparison of sales representatives' and physicians' responses *to direct statements*

Statement	Group	N	M	SD	Levene (F, sig)	T-test (t, sig)
2. Number of authorized indications for drug therapy	sales rep.	106	3.58	1.077	2.182	-0.345
	physician	155	3.63	1.207	0.141	0.730
6. Available guidelines for prescribing	sales rep.	106	4.00	0.986	0.002	-1.384
	physician	155	4.17	0.945	0.968	0.168
7. Opinions and recommendations of clinical pharmacists	sales rep.	106	2.64	1.475	0.396	-0.790
	physician	155	2.79	1.455	0.53	0.431
	sales rep.	106	3.60	0.813	7.408	2.263

13. Opinions and recommendations from peers	physician	155	3.34	1.053	0.007	0.024
14. Information about hospital prescribing practices	sales rep.	106	3.66	0.945	2.792	4.325
	physician	155	3.08	1.128	0.096	<0.001
23. Patients' requests for prescribing therapies	sales rep.	106	2.66	1.094	5.788	1.675
	physician	155	2.41	1.278	0.017	0.095
25. Medical studies	sales rep.	106	4.37	0.747	0.344	0.488
	physician	155	4.32	0.729	0.558	0.626

Table 18b Comparison of sales representatives' and physicians' responses to *drug-related statements*

Statement	Group	N	M	SD	Levene (F, sig)	T-test (t, sig)
1. Medical experience	sales rep.	106	4.68	0.469	7.934	1.666
	physician	155	4.56	0.675	0.005	0.097
3. Clinical efficacy of the therapy	sales rep.	106	4.57	0.552	14.464	-2.374
	physician	155	4.72	0.477	0.000	0.019
4. Therapy-related prescribing restrictions	sales rep.	106	3.63	0.949	3.186	0.584
	physician	155	3.55	1.112	0.075	0.560
5. Cost or cost level of the therapy relative to other therapies	sales rep.	106	3.25	1.005	0.002	0.426
	physician	155	3.20	1.028	0.967	0.670
8. Ease of administration, expected patient compliance	sales rep.	106	3.99	0.867	3.430	-0.490
	physician	155	4.05	1.062	0.065	0.624
9. Safety of drug therapy, side effect profile	sales rep.	106	4.44	0.731	0.773	-0.550
	physician	155	4.49	0.638	0.380	0.583
17. Availability of educational material about the therapy for patients	sales rep.	106	2.47	1.181	1.399	0.790
	physician	155	2.35	1.277	0.238	0.430
24. Drugs were developed in Hungary	sales rep.	106	3.33	1.058	10.606	2.468
	physician	155	2.95	1.441	0.001	0.014
33. Drugs are produced in Hungary	sales rep.	106	3.59	1.128	4.025	2.865
	physician	155	3.14	1.416	0.046	0.005

Table 18c Comparison of sales representatives' and physicians' responses *to indirect statements*

Statement	Group	N	M	SD	Levene (F, sig)	T-test (t, sig)
10. Availability of written professional information about the therapy, professional content	sales rep.	106	3.76	0.911	1.102	-2.040
	physician	155	3.99	0.879	0.295	0.042
11. Information received from pharmaceutical companies during drug detailing	sales rep.	106	4.38	0.668	3.058	5.961
	physician	155	3.77	0.896	0.082	<0.001
12. Information received from pharmaceutical companies during online detailing	sales rep.	106	2.51	1.165	1.283	-0.167
	physician	155	2.54	1.286	0.258	0.868
15. Drug samples provided by pharmaceutical companies	sales rep.	106	3.19	1.105	4.282	5.790
	physician	155	2.31	1.337	0.040	<0.001

16. Research support provided by pharmaceutical companies	sales rep.	106	3.60	1.066	15.883	7.444
	physician	155	2.45	1.447	<0.001	<0.001
18. Education, training programmes sponsored by pharmaceutical companies	sales rep.	106	3.58	1.042	5.163	5.657
	physician	155	2.76	1.275	0.024	<0.001
19. Pharmaceutical industry presence at professional events	sales rep.	106	3.28	1.067	3.643	4.931
	physician	155	2.55	1.255	0.057	<0.001
20. Advertisements in professional journals (paper and online)	sales rep.	106	2.72	1.102	2.554	4.447
	physician	155	2.04	1.279	0.111	<0.001
21. Quality of materials from sales representatives	sales rep.	106	3.56	0.794	18.664	7.180
	physician	155	2.66	1.213	<0.001	<0.001
22. Small gifts from pharmaceutical companies (pens, etc.)	sales rep.	106	2.95	1.027	9.774	12.087
	physician	155	1.26	1.217	0.002	<0.001
26. Visual appearance and packaging of drugs	sales rep.	106	1.97	1.246	0.654	4.790
	physician	155	1.23	1.210	0.419	<0.001
27. Slogans of pharmaceutical companies, brand associations	sales rep.	106	2.88	1.217	2.350	8.341
	physician	155	1.53	1.326	0.126	<0.001
28. Form of financing for a particular therapy	sales rep.	106	3.55	0.927	8.610	5.271
	physician	155	2.81	1.323	0.004	<0.001
29. Recommendations from recognized physicians, opinion leaders	sales rep.	106	4.08	0.912	19.705	5.734
	physician	155	3.28	1.318	<0.001	<0.001
30. Good relationship between physicians and sales representatives	sales rep.	106	4.70	0.520	52.770	11.022
	physician	155	3.51	1.186	<0.001	<0.001
31. Expertise of sales representatives	sales rep.	106	4.43	0.717	19.387	7.490
	physician	155	3.56	1.163	<0.001	<0.001
32. Stability of the pharmaceutical company (history)	sales rep.	106	3.99	1.046	13.931	5.321
	physician	155	3.19	1.390	<0.001	<0.001

In summary, the results suggest the following conclusions:

- The impact of drug-related factors (safety, efficacy, compliance, cost) on prescribing behaviour was evaluated similarly by physicians and sales representatives.
- Of the direct factors, the most important evaluation criteria concerning primary product attributes (professional experience, medical studies, guideline) are also viewed very similarly by physicians and sales representatives.
- The difference between the two groups in their perception of the impact on their prescribing behaviour is as follows:
    - With one exception, the indirect factors are typically marketing communication factors. The only exception is the ‘Impact of online detailing’, which is considered negligible by both groups. As for this factor, it is important to keep in mind that the COVID pandemic has had a significant impact on the marketing communication of the

pharmaceutical industry. For this reason, it would be interesting to explore the impact of online detailing on drug prescribing in more detail.

- Among the drug-related factors, those that have an impact at brand level (that is, not only the role of APIs but also that of the pharmaceutical company is important).
- For both sets of statements, sales representatives attribute much greater significance to the factors than physicians.

In the next step—now focusing on physicians only—factor analysis was used to group responses to the 33 statements into dimensions. A total of five statements were excluded from the factor analysis: three because their factor classification was not clear: [('3. Clinical efficacy of the therapy'; '9. Safety of the API therapy, side-effect profile'; '17. Availability of educational material about therapies for patients)']; and two because they had a relatively high average in the overall sample and would have constituted a separate factor: ('1. Medical experience'; '25. Medical studies') in the model of factors. Given their professional importance, four of the five statements (1, 3, 9, 25) are included in the analysis.

The factor analysis model was adequate, as confirmed by the statistics (KMO=0.826; Barlett $\chi^2(378) = 2324.228$; $p<0.001$). Total variance explained was also sufficiently high (64.22%), factor weights for each component are well fitted in each factor, their communality was sufficiently high and the internal consistency of all six factors reached a good level—see Appendix 4.

Following the factor analysis, 155 physicians were classified into five clusters using the factors and two independent statements (Table 19). The clusters are as follows:

- Fully informed (35)—physicians for whom almost everything is of above average importance, with the only exception of 'Professional type of marketing', which was rated as average. The 'Branding elements' factor stands out, with the highest value of 0.785 among the clusters, as well as '1. Medical experience' and '3. Clinical efficacy of the therapy' factors with an average of 5.000.
- 'Bureaucrats' (61)—for these physicians 'external validation' (0.264), 'compliance' (0.320), and 'efficacy of the therapy' (4.950) were the most important ones. 'Professional type marketing', on the other hand, is considered the least important one (-0.357).

- ‘Sensitive to brands and country of origin’ (33)—for these physicians the most important thing is that the drug is based in Hungary (0.291), and they also find the ‘Branding elements’ important (0.470). They are hardly affected by marketing communication and by the image of a professional and supported pharmaceutical company (-0.421), and—compared to the overall average and due to their low average of around 4—they are least concerned about their own medical experience (3.940), their medical studies (4.090), the efficacy of a therapy (4.000) and the safety of a drug therapy (4.150).
- ‘Efficiency seekers’ (19)—rely mostly on their medical experience (4.890), while they see regulations as least important (-1.335), and do not care whether drugs have any Hungarian roots (-0.736). Interestingly, ‘Safety of the drug therapy, side effect profile’, very different from the sample, and is regarded as the least important one (3.680).
- ‘Sensitive to drug detailing’ (7)—only seven people belong to this cluster, but they have extreme averages for all six factors and four statements. For them, medical experience (5.000) and medical studies (5.000) are essential, professional marketing is of high importance (1.914), they seem to need no external validation (-2.188), branding elements are also seen as not important (-1.418), they think that marketing communication and the reputation of the pharmaceutical company (0.721) is important, they comply with regulations (0.624), and whether a drug has Hungarian roots is unimportant to them (-0.566). Finally, the efficacy of the therapy (5.000) and safety of the drug therapy, and side-effect profile (4.710) are the most important factors.

Table 19 Statistics for the clusters formed according to the factors and the two statements

Cluster	N	Professional type of marketing	Marketing communication, professional and supported pharmaceutical company	External reinforcement (patients, peers, trade journals, price)	Regulations	Branding elements	Hungary	‘1. Medical experience’	3. Clinical efficacy of the therapy	9. Safety of drug therapy, side effect profile	25. Medical studies
Fully informed	35	0.041	0.481	0.289	0.408	0.785	0.102	5.000	5.000	4.860	4.660
Bureaucrats	61	-0.357	-0.126	0.264	0.320	-0.497	0.078	4.490	4.950	4.690	4.200
Sensitive to brands and country of origin	33	0.099	-0.421	-0.349	-0.388	0.470	0.291	3.940	4.000	4.150	4.090
Efficiency seekers	19	0.192	-0.016	0.032	-1.335	-0.145	-0.736	4.890	4.630	3.680	4.260
Sensitive to drug detailing	7	1.914	0.721	-2.188	0.624	-1.418	-0.566	5.000	5.000	4.710	5.000
Total	155	0	0	0	0	0	0	4.56	4.72	4.49	4.32
F (4;150)		10.826	5.142	15.347	20.047	22.896	4.372	18.587	79.159	22.601	5.179
Sig.		0	0.001	0	0	0	0.002	0	0	0	0.001
R-squared		0.2240	0.1206	0.2904	0.3484	0.3791	0.1044	0.3314	0.6785	0.3761	0.1213

First, the prescription frequency of different APIs was examined whether the frequency is different across the five clusters. In the first step, the Kolmogorov-Smirnov test was used to test for the normality of the data (see Tables 5a-c in Appendix 5), and then, based on the results, either the non-parametric Kruskal-Wallis test or the parametric analysis of variance was applied. Significant differences were found in several cases, as follows (see Tables 19a-c):

- Ramipril is generally included in one of six prescriptions as an API, except for with those 'Sensitive to drug detailing', who choose it only once in every twenty times.
- In the case of perindopril, the trend is quite the opposite: roughly one in two physicians use this API, while those 'Sensitive to drug detailing' use it two times out of three.
- Telmisartan is also popular with those who are 'Sensitive to drug detailing' (64.9%), while physicians in the other four clusters choose it only 3–4 times out of 10.
- Valsartan and losartan are popular—about 30% and 15%—with most physicians ('Fully informed', 'Bureaucrats', 'Sensitive to brands and country origin', 'Efficiency seekers'), whereas 'Sensitive to drug detailing' physicians use them very rarely (17.7% and 1.6% respectively).
- Although there is a statistically detectable difference between the five clusters for eprosartan, the low level of consumption of this drug makes the professional significance of the result negligible.

Table 19a Statistics and test results for prescription frequency of each API in the five clusters

Cluster	Stat.	ramipril	enalapril	fosinopril	lisinopril	perindopril	captopril	trandolapril	quinapril	benazepril
Fully informed (35 persons)	M	15.9%	5.7%	2.9%	16.7%	48.5%	7.2%	1.0%	1.2%	0.8%
	Me	17.0%	4.6%	0.0%	14.3%	46.8%	4.7%	0.0%	0.0%	0.0%
	SD	0.097	0.065	0.056	0.124	0.162	0.099	0.025	0.026	0.018
Bureaucrats (61 persons)	M	18.2%	6.2%	2.0%	16.6%	47.6%	6.9%	0.9%	1.3%	0.4%
	Me	18.1%	4.7%	0.0%	12.5%	49.1%	4.7%	0.0%	0.0%	0.0%
	SD	0.111	0.095	0.031	0.133	0.139	0.095	0.021	0.028	0.014
Sensitive to brands and country of origin (33 persons)	M	15.7%	9.1%	2.3%	14.5%	44.9%	8.8%	1.2%	2.5%	1.0%
	Me	12.8%	6.3%	0.0%	10.7%	43.8%	6.4%	0.0%	0.0%	0.0%
	SD	0.104	0.096	0.027	0.108	0.183	0.073	0.026	0.032	0.020
Efficiency seekers (19 persons)	M	18.2%	8.6%	2.0%	19.9%	44.7%	4.6%	0.7%	0.9%	0.6%
	Me	20.0%	6.0%	0.0%	7.9%	40.4%	5.9%	0.0%	0.0%	0.0%
	SD	0.132	0.085	0.031	0.216	0.183	0.032	0.020	0.022	0.017
Sensitive to drug detailing (7 persons)	M	4.6%	12.9%	0.7%	7.6%	68.5%	5.6%	0.0%	0.0%	0.0%
	Me	4.8%	7.1%	0.0%	5.5%	65.5%	5.5%	0.0%	0.0%	0.0%
	SD	0.061	0.096	0.020	0.052	0.106	0.054	0.000	0.000	0.000
Total (155 persons)	M	16.5%	7.3%	2.2%	16.1%	47.8%	7.0%	0.9%	1.5%	0.6%
	Me	16.7%	5.6%	0.0%	10.7%	46.8%	5.2%	0.0%	0.0%	0.0%
	SD	0.110	0.089	0.037	0.137	0.164	0.085	0.023	0.028	0.017
Kruskal-Wallis	H (4)	12.160	11.595	2.534	4.645	3,451*	4.740	2.230	9.622	6.031
	Sig.	0.016	0.021	0.639	0.326	0,010*	0.315	0.693	0.047	0.197

* ANOVA results are reported due to normality (Levene F(4;150)=0.889; p=0.472).

Table 19b Statistics and test results for prescription frequency of each API in the five clusters

Cluster	Stat.	candesartan	telmisartan	irbesartan	valsartan	losartan	olmesartan	eprosartan
Fully informed (35 persons)	M	4.0%	34.5%	12.9%	32.7%	13.1%	2.3%	0.5%
	Me	2.4%	31.3%	13.2%	30.0%	7.9%	0.0%	0.0%
	SD	0.065	0.176	0.085	0.191	0.109	0.061	0.014
Bureaucrats (61 persons)	M	2.7%	40.2%	13.3%	28.0%	13.8%	1.5%	0.6%
	Me	0.0%	37.3%	10.8%	26.7%	9.1%	0.0%	0.0%
	SD	0.046	0.203	0.103	0.167	0.116	0.029	0.038
Sensitive to brands and country of origin (33 persons)	M	3.1%	34.1%	15.2%	28.1%	15.2%	3.9%	0.3%
	Me	3.0%	31.9%	13.6%	28.0%	13.6%	0.0%	0.0%
	SD	0.036	0.155	0.095	0.127	0.104	0.070	0.014
Efficiency seekers (19 persons)	M	2.6%	47.1%	10.1%	24.7%	13.2%	2.0%	0.3%
	Me	0.0%	50.0%	7.9%	22.2%	9.4%	0.0%	0.0%
	SD	0.037	0.221	0.099	0.146	0.102	0.031	0.014
Sensitive to drug detailing (7 persons)	M	2.0%	64.9%	13.8%	17.7%	1.6%	0.0%	0.0%
	Me	0.0%	64.3%	16.1%	17.9%	0.0%	0.0%	0.0%
	SD	0.026	0.092	0.051	0.063	0.029	0.000	0.000
Total (155 persons)	M	3.0%	39.6%	13.3%	28.2%	13.3%	2.2%	0.4%
	Me	0.0%	36.8%	11.5%	26.7%	9.4%	0.0%	0.0%
	SD	0.047	0.197	0.095	0.161	0.110	0.049	0.026
Kruskal-Wallis	H (4)	2.108	20.215	3.698	2,734*	15.453	4.431	4.671
	Sig.	0.716	0.000	0.448	0,005*	0.004	0.351	0.323

* Results of Welch's d-test are reported due to normality (Levene F(4;150)=1.699; 0.153).

Table 19c Statistics and test results for drug-prescribing habits and attribute ranks in the five clusters

Cluster	Stat.	When you prescribe a drug, do you prefer to make your decision about a particular brand or a particular API?	Regulatory, institutional guidelines, protocols	Studies	Scientific medical literature	Scientific journals	Information from sales representatives	Peers' experiences, recommendations	Internet resources
Fully informed (35 persons)	M	3.714	3.200	2.400	2.686	4.086	4.029	4.829	6.771
	Me	4.000	2.000	2.000	2.000	4.000	4.000	5.000	7.000
	SD	1.202	2.336	1.499	1.301	1.721	1.014	1.224	0.490
Bureaucrats (61 persons)	M	3.869	3.246	2.770	2.213	3.410	4.705	4.885	6.770
	Me	4.000	3.000	3.000	2.000	3.000	5.000	5.000	7.000
	SD	1.008	1.972	1.838	1.002	1.383	1.358	1.082	0.668
Sensitive to brands and country of origin (33 persons)	M	3.667	3.424	2.121	2.818	4.333	4.515	4.788	6.000
	Me	4.000	3.000	2.000	2.000	4.000	5.000	5.000	7.000
	SD	0.924	1.985	1.386	1.758	1.407	1.661	1.516	1.521
Efficiency seekers (19 persons)	M	3.316	5.263	1.368	3.105	3.737	3.842	4.211	6.474
	Me	3.000	6.000	1.000	2.000	3.000	4.000	4.000	7.000
	SD	1.057	1.408	0.955	1.487	1.628	1.608	1.228	1.124
Sensitive to drug detailing (7 persons)	M	2.714	3.571	1.000	4.000	5.143	4.143	3.143	7.000
	Me	3.000	2.000	1.000	4.000	6.000	4.000	3.000	7.000
	SD	0.756	1.988	0.000	1.155	1.464	1.069	0.690	0.000
Total (155 persons)	M	3.671	3.535	2.297	2.639	3.877	4.381	4.690	6.581
	Me	4.000	3.000	2.000	2.000	4.000	5.000	5.000	7.000
	SD	1.058	2.087	1.612	1.381	1.556	1.406	1.272	0.979
Kruskal-Wallis	H (4)	12.051	15.739	19.311	13.397	14.598	10.028	15.752	14.118
	Sig.	0.017	0.003	0.001	0.009	0.006	0.040	0.003	0.007

Broadly similar results are produced when the normalized research results are compared with Hungarian market data; see Table 20. The difference is, however, significant as market results are higher for perindopril (67.3% vs 47.8%), while for lisinopril the questionnaire survey resulted in a much higher figure. In the case of lisinopril, the physician prescribing rate is almost four times as high as what market figures indicate (4.3% vs 16.1%). An explanation for this difference may be that, importantly, physician respondents were recruited for the survey with the help of the sales representatives of the pharmaceutical company. Another plausible explanation for the discrepancy may be that one of the lead products of the pharmaceutical company in this therapeutic category is a brand containing lisinopril. Thus, the phenomenon also provides an example of the impact of marketing communication.

Furthermore, perindopril was the most frequently selected of all the ACE therapies in segments where one of the pharmaceutical marketing elements has a strong influence. In the Hungarian market, perindopril sales account for 67.3% of the drug class (out of more than 10 APIs). The previous results show that ramipril and perindopril sales had a balanced market share in Hungary until 2016–2017, while ramipril dominance was observed in the studied EU markets. This correlation highlights the extent to which marketing efforts influence market patterns within a certain drug class. In conclusion, physicians' self-reported prescribing habits reflect the actual market trends adequately. This could serve as a basis for future research.

Table 20 Distribution of ACE inhibitors in physician prescriptions

API	Market results	Results of the questionnaire survey
ramipril	17.8%	16.5%
enalapril	6.7%	7.3%
fosinopril	0.9%	2.2%
lisinopril	4.3%	16.1%
perindopril	67.3%	47.8%
zofenopril	0.0%	0.0%
captopril	2.5%	7.0%
trandolapril	0.1%	0.9%
benazepril	0.1%	0.6%
quinapril	0.3%	1.5%
moexipril	0.0%	0.0%

The questionnaire included a question asking, 'Out of the ACE inhibitors and ARB inhibitors, which one do you prescribe more often to your patients?'. Respondents were given a choice of three answers to the question:

- I prescribe an ACE inhibitor to my patients in more than 50% of cases.
- I prescribe ACE inhibitors and ARB inhibitors in almost equal proportions.
- I prescribe an ARB inhibitor to my patients in more than 50% of cases.

There is no significant difference between the five clusters ($\chi^2(8)=13.278$; p=0.103) in terms of the responses to the question. However, when combining the clusters 'Bureaucrats', 'Sensitive to brands and country of origin', and 'Fully informed', the difference between the three clusters is significant ($\chi^2(4)=12.190$; p=0.016), which is reflected in the fact that the 'Sensitive to drug detailing' group consistently prefers ACE inhibitors (100%), while members of the 'Efficiency seekers' group prefer ACE inhibitors (31.6%) and are the least likely to prescribe ARB inhibitors (15.8%). About two-thirds (62.0%) of the members of the other three clusters prefer ACE inhibitors, one-third (32.6%) use both, and about one in twenty (5.4%) use ARB inhibitors (see Figure 32). The results confirm that Hungarian physicians largely use ACE inhibitors from the two therapeutic classes to treat hypertension. In forthcoming analysis, it may be worthwhile to use a finer scale to investigate this issue in detail.

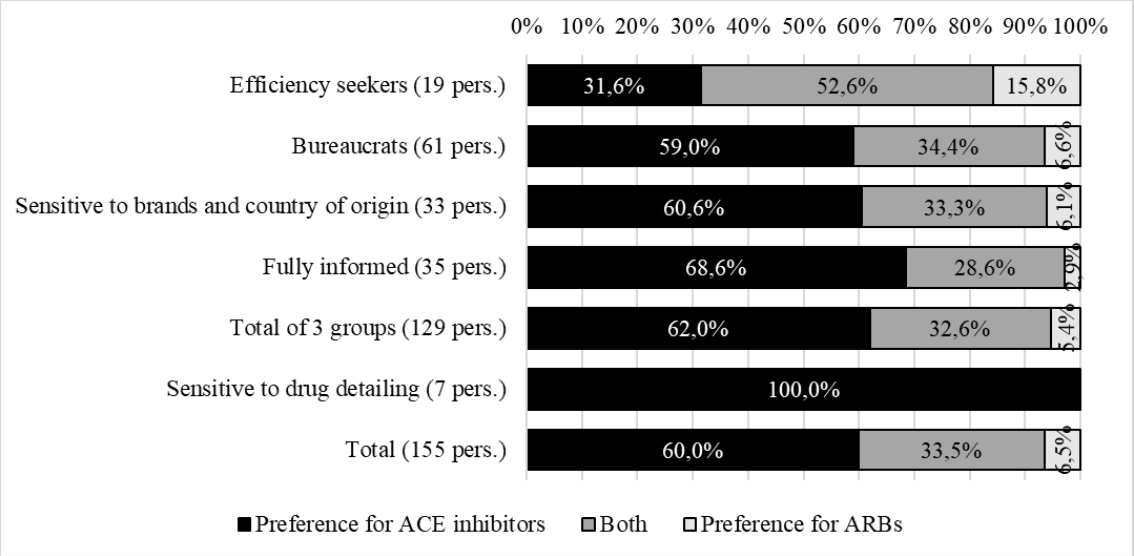


Figure 32 Distribution of physicians with a preference for ACE inhibitors and those with preference for ARB inhibitors by cluster

The comparison between physicians' and sales representatives' perceptions of drug choice within drug classes reveals that of the ACE inhibitors, the frequency of choice of ramipril and perindopril differs significantly between physicians and sales representatives; physicians think that they more often select them, while for captopril the difference is just the opposite; sales representatives think that physicians prescribe the drug more often than physicians think they do. These data also underline that perceptions about sales volumes differ significantly between industry and healthcare players, and individual perceptions within the two groups show high standard deviation. For ARB inhibitors—assuming high prescribing rates—the views on the sales volumes of valsartan are similar in the two groups. For telmisartan and losartan, sales representatives estimate a higher response rate than physicians. The Hungarian market was characterized by 31.9% sales of valsartan, 35.5% of telmisartan, and 19.6% of losartan in 2021.

It would be unprofessional to compare the results of Hungarian and US research (Nutescu) considering the numerical data only, as the circumstances were different and different target groups were interviewed, even if both studies included physicians. Physicians' statuses were different, the therapeutic area that the questions addressed was also different, and neither sample was representative of the relevant population. Yet the two surveys revealed similar trends, comparable in terms of physicians' views. In this respect, there are many similarities: in the US survey, FDA-approved indications—which can be seen as professional recommendation—are considered but physicians' experience with the drug, safety, costs, and prescribing guidelines were also considered important, at a similar or greater weight. In the Hungarian survey, the efficacy of the therapy is the highest rated factor, and similarly important influence is attributed to experience with the drug, safety, and prescribing guidelines. The trend is similar in both samples, although Hungarian data indicates that less importance is attached to cost-related factors. Another similar trend is that lesser importance is attributed to indirect variables, including the perception of pharmaceutical marketing, although other types of research and data indicate the higher impact of marketing promotions. There could be several underlying reasons for both samples—for example, pharmaceutical marketing may be less effective in this area, but the most plausible explanation is the presence of an 'expected response'; that is, physicians do not want to 'admit' that indirect factors affect them (Nutescu, 2005). In Hungary, drug detailing is a significant element of pharmaceutical companies' marketing efforts, which is rated as important by interviewees as well.

5. Discussion, conclusions

The market diffusion of innovative and generic drugs and changing preferences for prescription drugs is a highly complex process. Market positioning is determined by the attributes of the competing drugs and by the complex set of relationships between the players on the pharmaceutical market. Throughout the research, I have focused on the clinical appropriateness of drug therapies, and throughout the literature review and my research I have attempted to explore how clinical evidence exerts an influence and can determine market performance subsequently. For the qualitative research I defined a framework that combines evidence-based medicine with a marketing approach to address the main research question. Qualitative research results revealed that clinical appropriateness can play a role almost without exception for all factors that can determine sales at API level, but it is not by far the sole and dominant factor in the complex interrelationship among the purchasing decisions associated with the pharmaceutical industry. The impact of clinical evidence on market performance is believed to be distinctly more limited than that of factors that are mainly exerted at the brand level. For greater ease of interpretation and in-depth understanding, it is desirable to quantify these effects, for which I have developed a methodology within the framework of my marketing research.

By the time APIs become generic, they have been on the pharmaceutical market as innovations for decades. Genericization will considerably improve access to therapies for society by providing drugs at a lower price and by increasing the number of market players. It also means that there is much more extensive expertise on APIs—and on the whole class of APIs—than on completely new, pioneering therapies. Thus, the process of genericization accelerates the dissemination of information about clinical evidence. Considering the long-term change in aggregate sales volume, two conclusions can be drawn. On the one hand, the comparison of ARB and ACEI therapies reveals that the increasing dominance of ARBs in European markets ceased after 2009–2010, which, despite the decreasing price and clinical superiority of ARBs may be a negative outcome for patients. On the other hand, in contrast to the previous trend, ramipril was the most popular solution—based on the sales volume of ACE therapies—which is a positive result from the perspective of consumers and the ranking of evidence-based principles.

One of the most striking features of the time-series data is that, in Hungary, Romania and Poland, sales of the ARB drug class have grown in parallel with the introduction of generics, albeit slowly and from a low starting point. This trend cannot be confirmed for Western European countries except for Germany. Sales analysis revealed that, with the diffusion of generic drugs, ARB sales stagnated in Western countries in the 2010s. Despite the significant decrease in ARB prices, the market share of ACE inhibitors has remained virtually unchanged. It can be assumed that the initial diffusion of ARBs in most Western countries was not hindered by high prices, but that the availability of generic drugs has improved access to ARBs in the German and three Eastern European markets. A reasonable explanation for the flattening volume graphs for ARBs and ACE inhibitors in Western countries is that the Western markets that had started using ARBs earlier had become saturated by the middle of the research period, meaning that from then on the number of untreated patients requiring angiotensin drugs became negligible. This may be true for the Netherlands, the UK and Italy, where sales of ACE inhibitors and ARBs that had attained high coverage remained mostly unchanged over a longer period. In contrast, although ARB sales stagnated in Spain and France after 2010, sales of ACE inhibitors grew almost linearly. Presumably, an important factor behind this trend is the difference in the level of competition between the two classes of drugs. Until the 2010s, ARBs, with monopolistic position and high prices, competed at the level of APIs. Conversely, ACE therapies started to compete at the brand level much earlier, with increasing generic authorization and market entry, declining prices, and gaining ground against ARB therapies. Accordingly, the diffusion of therapeutic classes seems to be strongly influenced by the difference in the level of competition.

Both in France and Spain, the increase in expenditure in the 2000s led to regulations aimed at reducing spending on drugs (Avanzas et al., 2017; Chevreul et al., 2015). Looking again at the ARB volume shares in 2016, they were the highest in France and Spain at 50.63% and 51.66% respectively (slightly lower than in 2009). By contrast, the UK share was the lowest in 2016, at 22.71%. As regards the UK market, it is important to note that prior to 2011—according to the NICE recommendation (NICE Clinical Guideline, 2006; EHGD, 2004)—ARBs were only be recommended to be prescribed if there was intolerance or contraindication to ACE inhibitors. In 2011, the guideline was changed (NICE Clinical Guideline, 2011) and low-cost ARBs were recommended as first-line therapy. At the same time, the market share of ARBs in the UK has remained

essentially unchanged since 2005. The almost unchanged medium-term market share suggests that prescribing patterns are fixed, at least at the therapeutic class level. Results indicate that average manufacturer prices in the two therapeutic classes have been converging. In most countries, the reimbursement rates are the same (see Table 5) in the two therapeutic classes, so patients also perceive a price level decrease in line with manufacturers' prices, except for in Hungary, where reimbursement for ACE inhibitor and ARB therapies is different (80% and 55% respectively). This difference can also provide an explanation for the poor market performance of ARB therapies in comparison to ACE therapies.

Focusing on the investigation of ACEI therapies, the most important APIs have become generic in the nine countries in the 2000s. Competition has steadily shifted to the generic arena since the beginning of the period under review. Although low-selling APIs had no or very few competitors on the European markets, I would not consider this a significant distorting factor in general. The figures of 2016 reflect established market conditions of generics, albeit not necessarily perfect competition. The European markets under review are characterized by competition between ramipril and perindopril, with lisinopril and enalapril being significant players and the other APIs declining in importance. The diffusion of clinically preferred therapies has been strongly supported by the emerging generic competition, and price levels showed an inversely proportional trend with the increase in the number of brands. The results—aggregate data—indicate that ramipril has outperformed its competitors in the long term. The exceptions are found in Hungary, Romania, the Netherlands, and France, where perindopril has become the market leader in terms of volume, especially according to data from the years 2018 and 2021. The analysis reveals that while the price of ramipril has decreased significantly in all markets, the price decrease of perindopril, compared to ramipril, is less significant.

Figures also confirm that only innovative products with the similar or same efficacy and safety profile can compete on the pharmaceutical market. This phenomenon can be clearly seen in the case of captopril, which started with the decline in use as first-line therapy, then a subsequent decline to insignificance by the end of the period under review. Captopril has been replaced by clinically more appropriate therapies over the decades.

Denig's model explains that countries such as France, Spain, Italy, and the Netherlands are more likely to enter the typical medical 'evoked set' stage more efficiently when drugs

are still in the innovative phase, whereas in other countries such as Poland, Romania, and Hungary this process unfolds only after genericization. Alternatively, based on Rogers' innovation diffusion model, Eastern European countries can be considered late adopters of new ACE inhibitors and ARBs. However, it is doubtful whether the existence of late adopters is really related to uncertainty about new technology, as Rogers suggested, rather than to drug pricing. It should also be considered that manufacturers tend to enter markets that indicate higher potential and concentrate their marketing resources there. Figure 33 provides an excellent illustration of the above and shows the trend in the changes from 2006 to 2011. The graph reveals that while in Germany almost every single product (both generic and innovative) approved by the European Medicines Agency is authorized, the share is only between 50-55% in Poland and the Netherlands and barely above 35% in Portugal. The graph indicates that the more purchasing power a country has, the more competitors are present on the pharmaceutical market. On the regulatory side, it is very interesting to note that while in Germany the average duration to market a drug after authorization is 2–3 months, while in several other countries it is close to or even more than 12 months (IT, ES, FR, NL). The duration between authorization and market entry depends mainly on the length of time needed to obtain reimbursement.

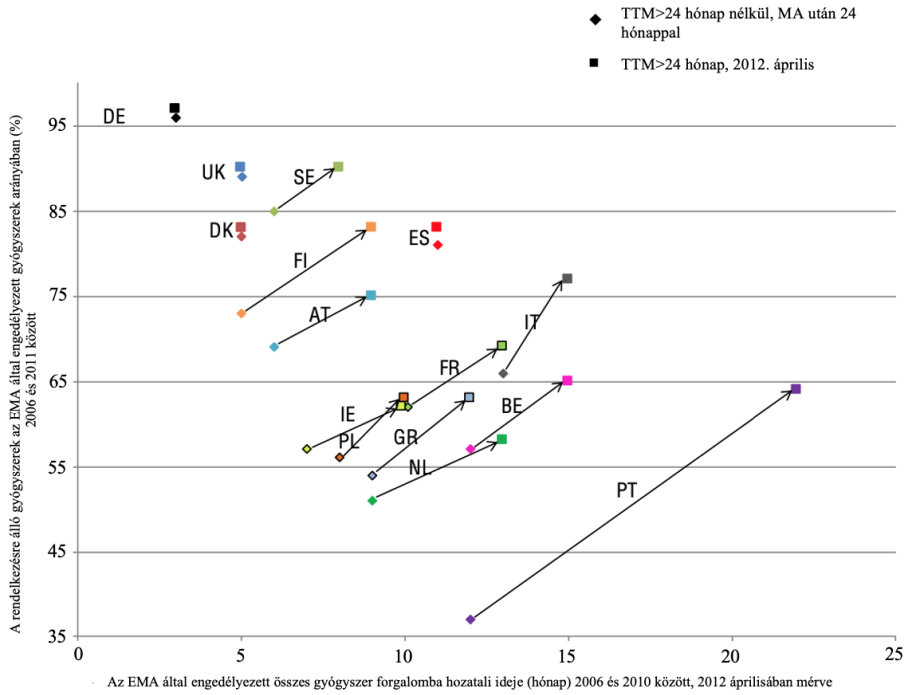


Figure 33 Average duration to market of EMA-authorized drugs and change of duration, percentage share of European-Medicines-Agency-approved therapies and change of share in each country, 2006–2011

The availability of drug stocks in each country will certainly be improved by the regulatory stringency of recent years, whereby a new API can only be authorized through a centralized procedure at the EMA. (This was not the case in the period under review.)

The analysis of the secondary data revealed that the impact of marketing activities can only be interpreted to a limited extent using API-level aggregated data, therefore it is suggested to investigate data at the brand level. The results indicate a country-of-origin effect in several cases, for example for perindopril, lisinopril and zofenopril. The market share of perindopril in France, Romania and Hungary was significant for most of the studied period, but the rate of change in market share was slightly different. In France, the share hardly changed since 2009, then perindopril became the dominant ACE therapy in the late 2010s. In the Hungarian market, the growth rate of perindopril's share accelerated from the late 2000s and has been steadily increasing since. In Romania, growth has been almost linear since the early 2000s. The number of perindopril brands on the market increased dramatically between 2008 and 2010, suggesting that the arrival of generic competition had a major impact on the diffusion of APIs in Hungary, while in France—similarly to with ramipril—growth came to a stop following the entry of perindopril generics. In Romania, the entry of generics had little impact on the market dynamics of perindopril diffusion. However, in the Hungarian, Polish and Romanian markets, ramipril's market share increased—similarly to that of ARBs—in line with price reductions and the arrival of generic competition. This suggests that in the three Eastern European countries the diffusion of new therapies was less influenced by marketing communications from innovative manufacturers than by price competition due to the market launch of generics, which allowed for the more extensive use of more advanced therapies. Interestingly, even in the cost-conscious UK market, which was heavily dominated by ramipril, revenue-based data suggest that marketing communications for perindopril slowed down the diffusion of the generic and low-cost ramipril until the start of genericization. Perindopril-related litigation cannot be left out of the evaluation about competition. In addition to the other important factors described above, the—highly unlawful—inhibition of competition may have had an important impact on the development of market performance in Europe.

In conclusion, genericization in Eastern European countries has not only improved access to ACE inhibitors and ARBs but has been a precondition for a change in preferences. In contrast, APIs genericization in some Western European countries has resulted in a

relative anchoring of preferences, a phenomenon that can be explained by the reduced marketing communication of innovative products.

The temporal variation of the Herfindahl-Hirschman index (HHI) is somewhat similar in the three Central and Eastern European countries, especially compared to in Western countries. From the early 2000s onwards, the HHI for manufacturing and sales revenues shows a decreasing concentration, which reversed after 2006–2007. In contrast, French, German, and British data show a near-constant increase in market concentration as regards the market share of APIs. This is mainly due to the steady decrease in the large share of enalapril (and captopril in Romania) in the early 2000s. Thus, the market share of more advanced therapies (ramipril, lisinopril, and perindopril) was greater in the three Western countries than in the Eastern European countries, where the older and cheaper APIs were initially more prevalent.

Consequently, the interplay between clinical evidence and market performance is strongly distorted by several factors, with prescribing physicians playing a key role. An evaluation of the various factors that influence physicians' perceptions is key to understanding the trends that ultimately lead to the prescription of different APIs and their market performance. Consequently, the marketing research was constructed on the results of the qualitative research.

To measure the impact of these factors, I conducted a quantitative survey among physicians and sales representatives using a non-representative sample. The impact of factors describing physicians' decisions was measured with the use of the validated scale created by Nutescu et al. and the list of statements were extended based on the results of my qualitative research.

Physicians generally consider drug-related and direct types of information as the most important decision-influencing factors that convey professional data and facts originating either from their own studies or from prescribing guidelines or from sales representatives. Research results demonstrate that physicians consider information acquired through marketing tools as less important. In contrast, our results point out the significant impact of marketing activities on the market share of APIs, highlighting the diffusion of perindopril sales in the domestic market as an example.

Based on physicians' views, the most important dimensions were identified, and, on this basis, physicians' behaviour was segmented. The analysis of the segments indicates that marketing factors play a significant role, in addition to professional aspects.

The opinions of physicians and sales representatives seem to differ significantly for several factors, mainly related to marketing activities, where the phenomenon of expected responses may distort the responses. The novelty of the questionnaire survey is that it examines physicians' and sales representatives' perceptions side by side, thus providing an opportunity to compare professional and industry perspectives. The questionnaire survey also included questions about prescribing specific drugs. The findings could be compared with real market data on sales volumes. I have identified two examples where there was a significant difference between the two sets of data (sales of lisinopril and perindopril). In both cases, the distorting effect of marketing activities is assumed to have led to bias.

I believe that the major achievement of my doctoral research is the theoretical framework that attempts to describe the interplay between clinical evidence and marketing performance in detail. A schematic diagram of the conceptual and analytical framework is presented in the last figure. The figure reveals how the diffusion of pharmaceutical therapies takes place, and what I suggest is investigating the market patterns that occur as a result of competition (cross-sectional and longitudinal analysis of secondary data at API and brand level in a sample across several countries). Market diffusion is linked to the principles of evidence-based medicine, Rogers' diffusion model, and Porter's value-based health service model (the dominant theories are marked in purple in the figure). The most influencing prescribing factors were systematically identified in the qualitative research and the extent of the influence of these factors was explored through primary marketing research. The findings were interpreted in such a way that the effects of pharmaceutical regulation and policy, as well as the effects of marketing activities, are incorporated in the evaluation. Since the market performance of drug therapies is explained as a result of physicians' prescribing decisions, secondary market data and findings of the primary marketing research are compared and contrasted, and prescription-influencing factors are examined in terms of cause-and-effect relationships with market performance data. (In the figure, green colours symbolize my analyses, while blue colours symbolize the body of knowledge detailed in the literature review of the doctoral research.) I believe that in the pharmaceutical industry general conclusions at the API level can only be drawn in

their complexity and by linking disciplines. In addition to the theoretical and practical recommendations, and with regard to the therapeutic regimens for hypertension, an analysis of two API classes with different mechanisms of action is also carried out. I believe that the framework thus constructed is applicable in the analyses of any similar therapeutic drug class (e.g., antipsychotics, diabetes drugs, contraceptives, etc.).

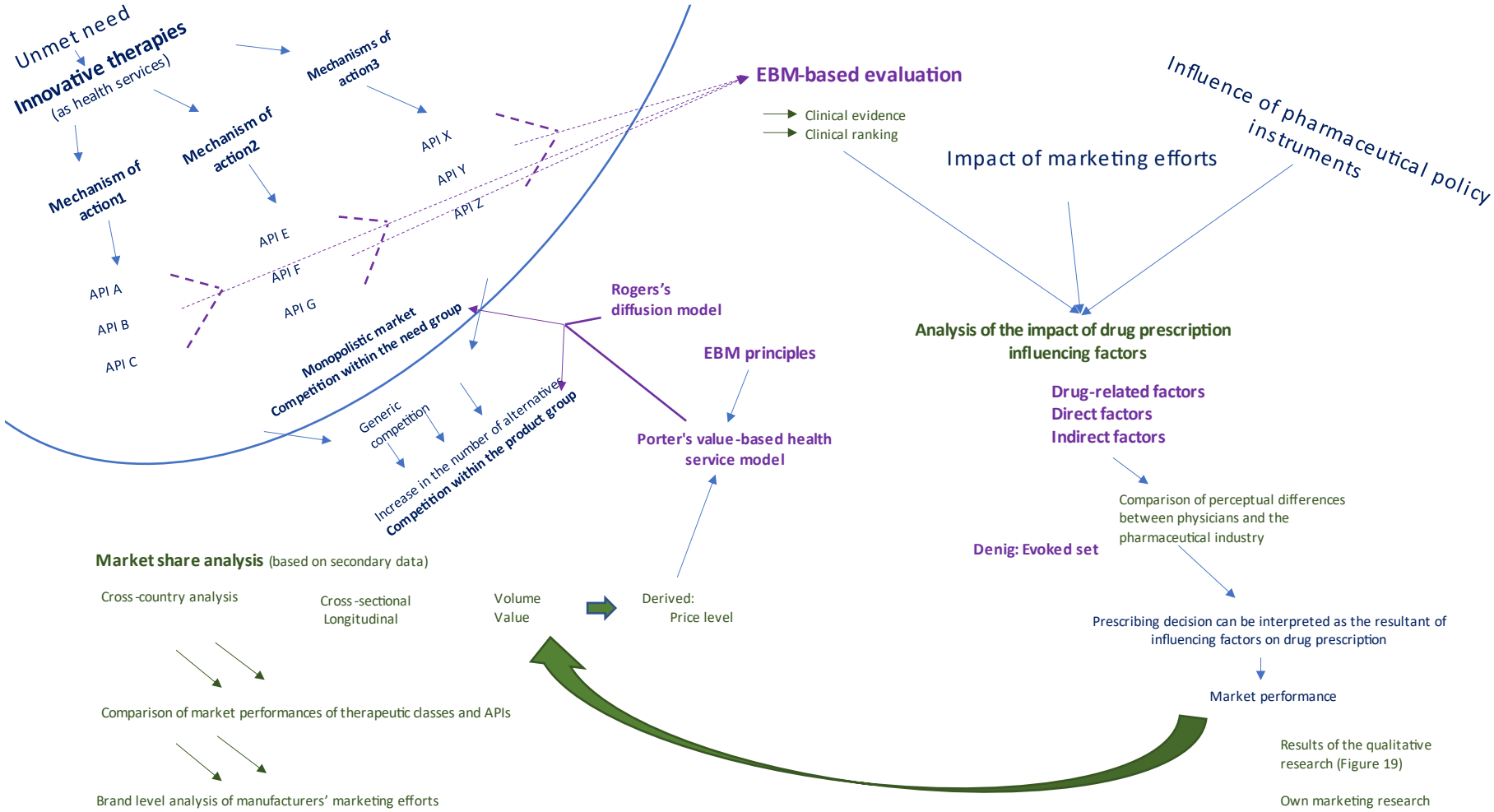


Figure 34 Schematic diagram of the conceptual and analytical framework resulting from the doctoral research

Reference list

2005. évi XCV. törvény az emberi alkalmazásra kerülő gyógyszerekről és egyéb, a gyógyszerpiacot szabályozó törvények módosításáról.

2017 Global life sciences sector outlook | Life Sciences and Health Care reports.

Ab E., Denig P., van Vliet T., Dekker J. H. (2009): Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: a qualitative study. BMC Fam Pract 10:24

Abrantes-Metz R. M., Adams.Ch.P., Metz. A. D. (2005): Empirical facts and Innovation markets: Analysis of The Pharmaceutical Industry, March 2005

Abzakh A.A., Ling K.C., Alkilani K. (2013): The impact of perceived risks on the consumer resistance towards generic drugs in the Malaysia pharmaceutical industry. Int. J. Bus. Manag., 8, 42–50.

Achrol R. S, Kotler Ph. (1999): Marketing in the Network Economy. Journal of Marketing, Vol. 63, Special Issue, 143–163.

Ahmed, R. R., Vveinhardt, J.; Štreimikiene, D.; Awais, M. (2016): Mediating and Marketing factors influence the prescription behavior of Physicians: An Empirical Investigation. Amfiteatru Econ., 18, 153–167.

Ajzen I. (1991): *The theory of planned behaviour*, Organ Behav Hum Decis Process, 50, pp.179-211.

Allan, G. M., Lexchin, J., Wiebe, N. (2007). Physician awareness of drug cost: a systematic review. PLoS medicine, 4(9), e283.

Alpern J. D., Stauffer W. M., Kesselheim AS (2014): High-Cost Generic Drugs — Implications for Patients and Policymakers. N Engl J Med 371:1859–1862

Anderson B. L., Silverman G. K., Loewenstein G. F., Zinberg S., Schulkin J. (2009): Factors Associated with Physicians' Reliance on Pharmaceutical Sales Representatives. Acad Med 84:994–1002

Andersson K., Petzold M. G., Sonesson C., Lönnroth K., Carlsten A. (2006): Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trends in Sweden 1986–2002. Health Policy.;79(2):231-43.

Andriska, P., Komáromi, T. (2019): Nincs már benne újabb hajtóerő. https://www.marketingpirula.hu/cikkek/nincs-mar-benne-ujabb-hajtoero/ [Downloaded: 2021.09.30.]

Antalóczy K. (1997): A magyar gyógyszeripar versenyképessége - adatok, hipotézisek, töprengések. A „Versenyben a világgal" - A magyar gazdaság versenyképességének mikrogazdasági tényezői c. kutatási program MUHELYTANULMÁNY sorozata.

Arcaro R., da Veiga C. R. P., da Silva W. V., Pereira da Veiga C. (2021): Attitude and Purchase Intention to Generic Drugs. International Journal of Environmental Research and Public Health.; 18(9):4579. https://doi.org/10.3390/ijerph18094579

Arcidiacono P., Ellickson P., Landry P., Ridley D. (2013): Pharmaceutical Followers. doi: 10.3386/w19522

Atella V., Peracchi F., Depalo D., Rossetti C. (2006): Drug compliance, co-payment and health outcomes: evidence from a panel of Italian patients. Health Econ.; 15(9):875-92.

Aufegger L., Yanar C., Darzi A., Bicknell C. (2021): The risk-value trade-off: Price and brand information impact consumers' intentions to purchase OTC drugs. J. Pharm. Policy Pract., 14, 11.

Avanzas P., Pascual I., Moris C. (2017): The great challenge of the public health system in Spain. J Thorac Dis 9:S430–S433

Azoulay P. (2002): Do Pharmaceutical Sales Respond to Scientific Evidence? J Econ Manag Strateg 11:551–594

Azoulay, P. (2002): Do pharmaceutical sales respond to scientific evidence? Journal of Economics & Management Strategy, 11(4), 551-594.

Bahrinizadeh M., Esmaiilpoor M., Haraghi M. (2014): Brand Equity and Country of Origin Model in Pharmaceutical Industry. Kuwait Chapter of Arabian Journal of Business and Management Review, 3 (6), pp.137-146.

de Bakker D. H., Coffie D. S. V., Heerdink E. R., van Dijk L., Groenewegen P. P. (2007): Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. BMC Health Serv Res 7:132

Barbu, A. (2012). Prescription at INN Level in Romanian Pharmacies: an Application of Latin Square Designs.

Barros P. P., Nunes L. C. (2010): The impact of pharmaceutical policy measures: an endogenous structural- break approach. Soc Sci Med.;71(3):440-50.

Bartus, Gy., Hankó, Z. (2011): hatályba lép a generikus ösztönző rendszer – MGYK. https://www.mgyk.hu/hatalyba_lep_a_generikus_osztonzo_rendszer_-_mgyk.html [Downloaded: 2021.09.30.]

Basak, R., Bentley, J.P., Mccaffrey, D.J., Bouldin, A.S., Banahan, B.F. (2015): The role of perceived impact on relationship quality in pharmacists' willingness to influence indication-based off-label prescribing decisions. Soc. Sci. Med. 2015, 132, 181–189.

Bauer, A., Beracs, J., Kenesei, Zs. (2016): Marketing alapismeretek. 10.1556/9789630597364.

Becker, M.C., Lillemark, M. (2006): Marketing/R&D integration in the pharmaceutical industry. Research Policy. Vol 35. Issue 1.

Backhaus, K., Erichson, B., Weiber, R. (2015): Fortgeschrittene multivariate Analysemethoden, 3. Auflage, Springer Gabler Verlag, p. 454

Belloni A., Morgan D., Paris V. (2016): Pharmaceutical Expenditure And Policies. doi: 10.1787/5jm0q1f4cdq7-en

Bergua L., Cartier T., Célant N., Pichetti S., Sermet C., Sorasith C. (2012): How to Explain Price Gaps between Me-too Drugs. Quest. d'économie la santé Irdes

Berndt, E. R., Bhattacharjya A., Mishol D.N., Arcelus A., Lasky T. (2002): An analysis of the diffusion of new antidepressants: variety, quality, and marketing efforts. J Ment Health Policy Econ 5:3–19

Berndt, E. R., Pindyck R. S., Azoulay P. (2003): Consumption Externalities and Diffusion in Pharmaceutical Markets: Antiulcer Drugs. J Ind Econ 51:243–270

Berndt, E. R., Bui, L. T., Lucking-Reiley, D. H., & Urban, G. L. (1996): The roles of marketing, product quality, and price competition in the growth and composition of the US antiulcer drug industry. In The economics of new goods (pp. 277-328). University of Chicago Press.

Blaskó Gy. (2011): Válogatott fejezetek a gyógyszerügyi managementből, Debreceni egyetem gyógyszerügyi management és szervezés tanszék, pp. 22.

Bongers F., Carradinha H. (2009): How to increase patient access to generic medicines in European healthcare systems. EGA Health Economics Committee. Eur. Generic Med. Assoc., 1–52.

Bootman, J. L., Townsend, R. J. (1991): Principles of pharmacoeconomics. Harvey Whitney Books.

Borjádi, Gy., Juhász, P. (2003): Marketingpirula recept nélkül, Galenus Kiadó, Budapest 2003.

Borsi, B., Demeter, Á., Szalkai, Zs., (2004): A vállalatok és az egyetemek kapcsolata a magyarországi gyógyszeripari kutatás-fejlesztésben. VIII. Ipari- és Vállalatgazdasági Konferencia, Pécs

Botz, L. (Ed.), (2014): A gyógyszerterápia bizonyítékokon és gyógyszeradatbázisokon alapuló értékelésének gyakorlata, Pécsi Tudományegyetem

Botz, L., Szűcs, F., (2008a): A bizonyítékon alapuló orvoslás gyógyszerértékelési szempontjai és gyógyszerészeti vonatkozásai 1., Gyógyszerészet 52, 67-71

Botz, L., Szűcs, F., (2008b): A bizonyítékon alapuló orvoslás gyógyszerértékelési szempontjai és gyógyszerészeti vonatkozásai 2., Gyógyszerészet 52, 195-200

Bradley, C. P. (1992): Factors which influence the decision whether or not to prescribe: The dilemma facing general practitioners. Br J Gen Pract 42:454–458

Brekke K. R., Grasdal A. L., Holmas T. H. (2009): Regulation and pricing of pharmaceuticals: Reference pricing or price cap regulation? Eur. Econ. Rev., 53, 170–185.

Campo, K., Staebel, O. D., Gijsbrechts, E., & Van Waterschoot, W. (2005). Physicians' decision process for drug prescription and the impact of pharmaceutical marketing mix instruments. Health marketing quarterly, 22(4), 73-107.

Carthy, P., Harvey, I., Brawn, R., Watkins, C. H. (2000): A study of factors associated with costs and variation in prescribing among GPs. Family Pract., 17, 36–41.

Caudill, T. S., Johnson, M. S., Rich, E. C., McKinney, W. P. (1996): Physicians, pharmaceutical representatives, and the cost of prescribing. Arch Fam Med. 1996; 5(4):201-6.

Chevreul, K., Berg Brigham K., Durand-Zaleski, I., Hernandez-Quevedo, C. (2015) France: Health System Review. Health Syst. Transit.

Chintagunta, P. K., Desiraju, R. (2005): Strategic pricing and detailing behavior in international markets. Marketing Science.24 (1) 67-80.

Clauson, K.A., Seamon, M. J., Clauson, A. S., Van, T. B. Evaluation of drug information databases for personal digital assistants. Am J Health Syst Pharm 2004;61:1015-24.

Claxton, K., Sculpher, M., Carroll, S. (2011): Value-based pricing for pharmaceuticals: its role, specification and prospects in a newly devolved NHS. (CHE Research Paper; No. 60). Centre for Health Economics, University of York.

Conti, R., Berndt, E. (2014): Specialty drug prices and utilization after loss of U.S. patent exclusivity, 2001-2007. doi: 10.3386/w20016

Crawford, G. S., Shum, M. (2005): Uncertainty and learning in pharmaceutical demand. Econometrica 73:1137–1173

Cutler, D. M., Berndt, E. R. (Eds.). (2007): Medical care output and productivity (Vol. 62). University of Chicago Press.

Damiani, G., Federico, B., Silvestrini, G., Bianchi, C. B., Anselmi, A., Iodice, L. et al. (2013): Impact of regional copayment policy on selective serotonin reuptake inhibitor (SSRI) consumption and expenditure in Italy. Eur J Clin Pharmacol.; 69(4):957-63.

Damiani, G., Federico, B., Anselmi, A., Bianchi, C. B., Silvestrini, G., Iodice, L. et al. (2014): The impact of regional co-payment and national reimbursement criteria on statins use in Italy: an interrupted time-series analysis. BMC Health Serv Res.; 14:6.

Dankó, D., Molnár, M. P. (2013): Gyógyszertámogatás, Medicina Könyvkiadó, pp.155-159.

Danzon, P. M., Furukawa, M. F. (2011): Cross-National Evidence on Generic Pharmaceuticals: Pharmacy vs. Physician-Driven Markets. Natl Bur Econ Res Work Pap Ser. doi: http://www.nber.org/papers/w17226.pdf

Darida, M. (2019): Az angiotenzin-receptor blokkolók és az angiotenzin-konvertáló enzim gátló hatóanyagok forgalmának alakulása egyes európai országokban a generikussá válás alatt és után

De Laat, E., Windmeijer, F., Douven, R. C. M. H. (2002): How does pharmaceutical marketing influence doctors' prescribing behaviour?. Den Haag: CPB.

De Vries, T. P. G. M., Henning, R. H., Hogerzeil, Hans V., Fresle, D. A., WHO Action Programme on Essential Drugs. et al. (1994). Guide to good prescribing: a practical manual / authors: T. P. G. M. de Vries ... [et al.]; with contributions from F. M. Haaijer-Ruskamp and R. M. van Gilst. World Health Organization. https://apps.who.int/iris/handle/10665/59001

Decsi, T. (2011): A bizonyítékokon alapuló orvoslás, Medicina könyvkiadó zrt. pp.97-101.

Denig, P., Witteman, C. L. M., Schouten, H. W. (2002): Scope and nature of prescribing decisions made by general practitioners. Qual Saf Health Care 11:137–43

Denig, P. (1994): Drug choice in medical practice: rationales, routines and remedies. s.n.

Desai, R. J., Sarpatwari, A., Dejene, S., Khan, N. F., Lii, J., Rogers, J. R., Dutcher, S. K., Raofi, S., Bohn, J., Connolly, J., et al. (2018): Differences in rates of switchbacks after sitching from branded to authorized generic and branded to generic drug products: Cohort study. BMJ, 361, k1180.

DiMasi, A. J., Hansen, R. W., Grabowski, H. G. (2003): The price of innovation: new estimates of drug development costs, Journal of Health Economics, 22.

DiMasi, J. A., Faden, L. B. (2011): Competitiveness in follow-on drug R&D: a race or imitation? Nat Rev Drug Discov 10:23–27

DiMasi, J. A., Grabowski, H. G., Hansen, R. W. (2016): Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ 47:20–33

Dinicolantoniom, J. J., Lavie, C. J., O'Keefe, J. H. (2013): Not all angiotensin-converting enzyme inhibitors are equal: focus on ramipril and perindopril. Postgrad Med 125:154–168

Dolovich, L., Levine, M., Tarajos, R., Duku, E. (1999): Promoting optimal antibiotic therapy for otitis media using commercially sponsored evidence-based detailing: A prospective controlled trial. Drug Info J. 1999; 33:1067-77.

Donohue, J. , O'Malley, A. J., Horvitz-Lennon, M., Taub, A. L., Berndt, E. R., Huskamp, H. A. (2014): Changes in physician antipsychotic prescribing preferences, 2002-2007. Psychiatr Serv 65:315–22

Drozdowska, A., Hermanowski, T. (2016): Predictors of generic substitution: The role of psychological, sociodemographic, and contextual factors. Res Social Adm Pharm. Jan-Feb;12(1):119-129. doi: 10.1016/j.sapharm.2015.03.003. Epub 2015 Mar 27. PMID: 25935316.

Duflos, G., Lichtenberg, F. R. (2012): Does competition stimulate drug utilization? The impact of changes in market structure on US drug prices, marketing and utilization. Int Rev Law Econ 32:95–109

Dunne, S., Shannon, B., Dunne, C., Cullen, W. (2013): A Review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol. Toxicol., 14, 1.

Dunne, S. S., Dunne, C.P. (2015): What do people really think of generic medicines? A systematic review and critical appraisal of literature on stakeholder perceptions of generic drugs. BMC Med., 13, 173.

Dylst, P., Vulto, A., Simoens, S. (2012): How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing? Pharm Pract (Granada). 2012 Jan;10(1):3-8. doi: 10.4321/s1886-36552012000100002. Epub 2012 Mar 31. PMID: 24155810; PMCID: PMC3798161.

Eccles, M.P., Hrisos, S., Francis, J., Kaner, E.F., Dickinson, H.O., Beyer, F., Johnston, M. (2006): Do self-reported intentions predict clinicians' behaviour: a systematic review, Implement Sci, pp. 1-28.

Eccles, M., Grimshaw, J., Shekelle, P., Schunemann, H., Woolf, S. (2012): Developing clinical practice guidelines: Target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Implement. Sci. 2012, 7, 60.

Egészségtudományi fogalomtár: Bizonyítékon Alapuló Orvoslás (BAO): https://fogalomtar.aeek.hu/index.php/Bizony%C3%ADt%C3%A9kon_Alapul%C3%B3_Orvosl%C3%A1s_(BAO) [Downloaded:2020. 11. 08.]

EHGD, Group N of (2004): Essential hypertension: managing adult patients in primary care.

Eisenhardt, M. (1989): Agency theory: And assessment review. Acad. Manag. Rev. 1989, 14, 57–74.

Elhayany, A., Vinker, S. (2011): Addressing healthcare inequities in Israel by eliminating prescription drug copayments. Am J Manag Care.; 17(7):e255-9.

European Commission (2009): Pharmaceutical Sector Inquiry Final Report.

European Medicines Agency (2020a): Generic medicine. https://www.ema.europa.eu/en/glossary/generic-medicine [Downloaded: 2021. 09. 18.]

European Medicines Agency (2020b): Generic and hybrid medicines. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines [Downloaded: 2021. 09. 18.]

Fabiano, V., Mameli, C., Cattaneo, D., Delle Fave, A., Preziosa, A., Mele, G., Clementi, E., Zuccotti, G. V. (2012): Perceptions and patterns of use of generic drugs among Italian family pediatricians: first round results of a web survey. Health Policy. 2012;104(3):247–52.

Fekete, F. (2013): Evidence based medicina a gyakorlati betegellátásban. Heim Pál Gyermekkórház: http://medicalonline.hu/gyogyitas/cikk/evidence_based_medicina_a_gyakorlati_betegellatasban [Downloaded: 2020.11.08.]

Ferech, M., Coenen, S., Malhotra-Kumar, S., Dvorakova, K., Hendrickx, E., Suetens, C. et al. (2006): European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. J Antimicrob Chemother.; 58(2):401-7.

Ferreira, P., Barbosa, H. (2017): Choice of mandatory prescribed drugs in Portugal: A consumers' perspective International. J. Pharm.Healthc. Mark., 11, 439–454.

Ferreira, V. L., Da Veiga, C.R.P., Kudlawicz-Franco, C., Scalercio, P., Da Veiga, C.P. (2017): Generic drugs in times of economic crisis: Are there changes in consumer purchase intention? J. Retail. Consum. Serv., 37, 1–7.

Fickweiler, F., Fickweiler, W., Urbach, E. (2017): Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: A systematic review. BMJ Open. doi: 10.1136/bmjopen-2017-016408

Figueiras, M.J., Marcelino, D., Cortes, M. A. (2008): People's view on the level of agreement of generic medicines for different illnesses Pharmacy. World Sci., 30, 590–594.

Finn, M. (2016): 2016 Top Markets Report: Pharmaceuticals.

Fiorio, C. V., Siciliani, L. (2010): Co-payments and the demand for pharmaceuticals: evidence from Italy. Econ Model.;27(4):835-41.

Fischer, K. E., Stargardt, T. (2016): The diffusion of generics after patent expiry in Germany. Eur. J. Health Econ., 17, 1027–1040.

Fischer, M., Leeflang, P. S. H., Verhoef, P. C. (2010): Drivers of peak sales for pharmaceutical brands. Quant Mark Econ 8:429–460

Fischer, M. A., Avorn, J. (2004): Economic Implications of Evidence-Based Prescribing for Hypertension: Can Better Care Cost Less? J Am Med Assoc 291:1850–1856

Food and Drug Administration. Generic Drugs Facts. 2018. Available online: https://www.fda.gov/drugs/generic-drugs/generic-drug-facts[Downloaded: 2021.01.12.].

Fornell, C. (1992): A National Customer Satisfaction Barometer: The Swedish Experience. Journal of Marketing, 56(1), 6–21. https://doi.org/10.1177/002224299205600103

Friedland, D. F. (ed., 1998): Evidence-based medicine, A Framework for Clinical Practice, Appleton and Lange, Stamford

Furberg, C. D., Pitt, B. (2001): Are all angiotensin-converting enzyme inhibitors interchangeable? J Am Coll Cardiol 37:1456–1460

Furberg, C. D., Psaty, B. M. (2003): Should Evidence-Based Proof of Drug Efficacy be Extrapolated to a “Class of Agents”? Circulation 108:2608–2610

Furberg, C., Furberg, B., Sasich, L. (2010): Knowing Your Medications, How do physicians decide when to prescribe a medication? Potata Inc. pp.3-6.

Furberg, C. D., Furberg, B. D., Sasich, L. D. (2016). Knowing Your Medications. Potata Inc.

Gallan, A. S. (2004): Factors That Influence Physicians’ Prescribing of Pharmaceuticals: A Literature Review Journal of Pharmaceutical Marketing & Management, Vol. 16 (4) pp.3-46.

Ganther, J. M., Kreling, D. H. (2000): Consumer perceptions of risk and required cost savings for generic prescription drugs. J. Am. Pharm. Assoc., 40, 378–383.

Garattini, L., Padula, A. (2018): Hospital Pharmacists in Europe: Between Warehouse and Prescription Pad?. PharmacoEconomics - open, 2(3), 221–224. https://doi.org/10.1007/s41669-018-0069-0

Garattini, L., Padula, A., Freemantle, N. (2021): Do European pharmacists really have to trespass on medicine?. Eur J Health Econ 22, 1–4, 2021. https://doi.org/10.1007/s10198-020-01185-w

Gemmill, M. C., Thomson, S., Mossialos, E. (2008): What impact do prescription drug charges have on efficiency and equity? Evidence from high-income countries. Int J Equity Health.;7:12.

Ghislandi, S., Krulichova, I., Garattini, L. (2005): Pharmaceutical policy in Italy: Towards a structural change? Health Policy, 72, 53–63.

Gill, L., Helkkula, A., Cobelli, N., White, L. (2010): How do customers and pharmacists experience generic substitution? Inter J Pharm Healthcare Mark. 2010; 4(4):375–95.

Girdharwal, N., Singh, A. (2007): A Study of Physicians Behaviour toward Marketing of Pharmaceutical Products (A Case Study of Indian Market, Vol.5, Issue, 6, 2007.

Godin, G., Belanger-Gravel, A., Eccles, M., Grimshaw, J. (2008): Healthcare professionals' intentions and behaviours: A systematic review of studies based on social cognitive theories, US National Library of Medicine, US National Institutes of Health.

Godman, B., Persson, M., Miranda, J., Skiold, P., Wettermark, B., Barbui, C. et al. (2013): Changes in the utilization of venlafaxine after the introduction of generics in Sweden. Appl Health Econ Health Policy.; 11(4):383-93.

Goldman, D., Joyce, G., Zheng, Y. (2007): Prescription drug cost sharing: associations with medication and medical utilization and spending and health, JAMA, Vol. 298/1, pp. 61-69, http://dx.doi.org/10.1001/jama.298.1.61.

Gómez, M., Rozano, M. (2012): Consumer dynamics in a nonmature generic drugs market: A causal model explaining intention to purchase in Spain. Drug Inf. J., 46, 207–215.

Gonzalez, J., Sismeiro, C., Dutta, S., Stern, P. (2008): Can branded drugs benefit from generic entry? The role of detailing and price in switching to non-bioequivalent molecules. Int J Res Mark 25:247–260

Gouya, G., Reichardt, B., Bidner, A., Weissenfels, R., Wolzt, M. (2008): Partial reimbursement of prescription charges for generic drugs reduces costs for both health insurance and patients. Wien Klin Wochenschr.;120(3-4):89-95.

Gönül F. F., Carter F., Petrova E., Srinivasan, K. (2001): Promotion of prescription drugs and its impact on physicians' choice behavior. Journal of Marketing. 65 (3) 79-90.

Grabowski, H. G., Kyle, M. (2007): Generic competition and market exclusivity periods in pharmaceuticals. Manag Decis Econ 28:491–502

Grabowski, H., Vernon, J., DiMasi, J. A. (2002): Returns on research and development for 1990s new drug introductions. Pharmacoeconomics 20 Suppl 3:11–29

Granlund, D. (2010): Price and welfare effects of a pharmaceutical substitution reform. J Health Econ.;29(6):856-65.

Greene, J.A., Kesselheim, A.S. (2011): Why do the same drugs look different? Pills, trade dress, and public health. N. Engl. J. Med., 365, 1.

Greving, J. P., Denig, P., van der Veen W. J., Beltman, F. W., Sturkenboom, M. C. J. M., Haaijer-Ruskamp, F. M. (2006): Determinants for the adoption of angiotensin II receptor blockers by general practitioners. Soc Sci Med 63:2890–2898

Gronde, T. V., Uyl-de Groot, C. A., Pieters, T. (2017): Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. PLoS One.; 12(8):e0182613. doi: 10.1371/journal.pone.0182613. PMID: 28813502; PMCID: PMC5559086.

Groves, K. E. M., Sketris, I., Tett, S. E.. (2003): Prescription drug samples–Does this marketing strategy counteract policies for quality use of medicines? J Clin Pharm Ther. 2003; 28(4):259-71.

Groves, K. (2006): The influence of pharmaceutical marketing activity, practice characteristics and physician profile on physician prescribing behavior. Ph.D. Dissertation, Dalhousie University, Halifax, NS, Canada.

Gummesson, E. (1995): Relationship Marketing: Its Role in the Service Economy. In: Glynn–Barnes (eds.): Understanding Services Management, Wiley, New York, 244–268.

Hadsall, R.S., Freeman, R.A., Norwood, G.J. (1982): Factors related to the prescribing of selected psychotropic drugs by primary care physicians, Soc SciMed, 16, pp. 1747-56.

Haider, M., Kreps, G. L. (2004): Forty years of diffusion of innovations: Utility and value in public health. J Health Commun 9:3–11

Hajjaj, F. M., Salek, M. S., Basra, M. K. A., Finlay, A. Y. (2010). Non-clinical influences on clinical decision-making: a major challenge to evidence-based practice. Journal of the Royal Society of Medicine, 103 (5) pp. 178-87.

Hamer, S., Collinson, G. (2014): Achieving evidence-based practice: A handbook for practitioners. Elsevier Health Sciences.

Hart, J., Salman, H., Bergman, M., Neuman, V., Rudniki, C., Gilenberg, D., Djaldetti, M. (1997). Do drug costs affect physicians' prescription decisions? Journal of internal medicine, 241(5), 415-420.

Hassali, M. A., Alrasheedy, A. A., Aljadhey, H. (2014): The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use. Saudi Pharm. J., 22, 491–503.

Haynes, R. B., Devereaux, P. J., Guyatt, G. H. (2002): Clinical expertise in the era of evidence-based medicine and patient choice. Evid Based Med 7:36–38

Health at a glance: Europe 2016. Paris: OECD Publishing; 2016 (http://www.oecd.org/health/ health-at-a-glance-europe-23056088.htm, [Downloaded: 2021.09.07.].

Heikkilä, R., Mäntyselka, P., Hartikainen-Herranen, K., Ahonen, R. (2007): Customers' and physicians' opinions of and experiences with generic substitution during the first year in Finland. Health Policy, 82, 366–374.

Heimans, L., Van Hylckama Vlieg, A., Dekker, F. W. (2010): Are claims of advertisements in medical journals supported by RCts? Neth J Med 68:46–49

Hepler, C.D., Clyne, K.E., Donta, S.T. (1982) Rationales expressed by empiric antibiotic prescribers, Am J HospPharm, 39, pp. 1647-55.

Hersh, A. L., Stefanick, M., Stafford, R.S. (2004): National use of postmenopausal hormone therapy. JAMA. 2004; 291:47-53.

Hess, J., Litalien, S. (2005): Battle for the market: Branded drug companies' secret weapons generic drug makers must know. J Generic Med 3:20–29.

Hoebert, J. M., Souverein, P. C., Mantel-Teeuwisse, A. K., Leufkens, H. G., van Dijk, L. (2012): Reimbursement restriction and moderate decrease in benzodiazepine use in general practice. Ann Fam Med.;10(1):42-9.

Hogerzeil, H. (1995): Promoting rational prescribing: An international perspective. Brit. J. Clin. Pharmacol., 39, 1–6.

Hogerzeil, H. V. (2006): Essential medicines and human rights: what can they learn from each other? Bull World Health Organ.; 84(5):371-5.

Hornecker, J. R. (2009): Generic drugs: History, approval process, and current challenges. U S Pharmacist., 34, 26–30.

Howard, J. N., Harris, I., Frank, G., Kiptanui, Z., Qian, J., Hansen, R. (2018): Influencers of generic drug utilization: A systematic review. Res. Soc. Adm. Pharm., 14, 619–627.

https://www2.deloitte.com/global/en/pages/life-sciences-and-healthcare/articles/global-life-sciences-sector-outlook.html. [Downloaded: 2020.12.29.]

Hudson, J. (2000): Generic take-up in the pharmaceutical market following patent expiry. Int Rev Law Econ 20:205–221

Hughes, J.W., Moore, M.J., Snyder, E.A. (2002): "Napsterizing" Pharmaceuticals: Access, Innovation, and Consumer Welfare. Natl. Bur. Econ. Res.

Hurwitz, M. A., Caves, R. E. (1988): Persuasion or information? Promotion and the shares of brand name and generic pharmaceuticals. The Journal of Law & Economics. 31 (2) 299-320.

Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE. In: August 2011, Last Updat. Novemb. 2016. https://www.nice.org.uk/guidance/cg127. [Downloaded: 2021.05.04.]

Jones, G. H., Carrier, M. A., Silver, R. T., Kantarjian, H. (2016): Strategies that delay or prevent the timely availability of affordable generic drugs in the United States. Blood 127:1398–1402

Joyce, G. F., Carrera, M. P., Goldman, D. P., Sood, N. (2011): Physician prescribing behavior and its impact on patient-level outcomes. Am J Manag Care 17: e462-71

Kaló, Z. (2010): Innovatív gyógyszerek fejlesztési és befogadáspolitikai kérdései. A magyar egészségÜGY Bodrogi József Budapest

Kanavos, P. (2014): Measuring performance in off-patent drug markets: A methodological framework and empirical evidence from twelve EU Member States. Health Policy (New York): 118:229–241

Kanavos, P., Costa-Font, J., Seeley, E. (2008): Competition in off-patent drug markets: Issues, regulation and evidence. Econ Policy 23:499–544

Kanitz, C., Burmann, C. (2012): The challenge of pharmaceutical brand architecture: A theoretical analysis based on the Brand Architecture Model (B.A.M.). The Marketing Review. 12. 10.1362/146934712X13420906885520.

Kaplan, W. A., Ritz, L. S., Vitello, M., Wirtz, V. J. (2012). Policies to promote use of generic medicines in low and middle income countries: a review of published literature, 2000–2010. Health Policy, 106(3), 211-224.

Kappe, E., Stremersch, S. (2016): Drug Detailing and Doctors' Prescription Decisions: The Role of Information Content in the Face of Competitive Entry. Mark Sci 35:915–933

Kauppinen-Räisänen, H., Owusu Richard, A., Abeeku, B. B. (2012): Brand salience of OTC pharmaceuticals through package appearance. Int. J. Pharm. Health Mark., 6, 230–249.

Kee, J., Khoo, H., Lim, I., Koh, M. (2018): Communication Skills in Patient-Doctor Interactions: Learning from Patient Complaints. Health Professions Education, 4(2), pp.97-106.

Keresztúri, J. L., Lublóy, Á., Benedek, G. (2014): Gyógyszerek terjedésének vizsgálata Cox-regresszióval. Statisztikai Szemle, 92:792–819

Kesselheim, A. S., Robertson, C. T., Myers, J. A., Rose, S. L., Gillet, V., Ross, K. M., Glynn, R. J., Joffe, S., Avorn, J. (2012): A Randomized Study of How Physicians Interpret Research Funding Disclosures. N Engl J Med 367:1119–1127

Kiss, I. (Editor) (2015): A hypertonia betegség ellátása - A Magyar Hypertonia Társaság ajánlása 2015. Hypertonia és Nephrol 19:1–38

Kobayashi, E., Karigome, H., Sakurada, T., Satoh, N., Ueda, S. (2011): Patients' attitudes towards generic drug substitution in Japan. Health Policy, 99, 60–65.

Koskinen, H., Ahola, E., Saastamoinen, L. K., Mikkola, H., Martikainen, J. E. (2014): The impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic medication in Finland. Health Econ Rev.; 4(1):9.

Kotler, Ph., Keller, K.L. (2012): Marketingmenedzsment (2012), Akadémiai Kiadó, p. 912

Kovács, B. (2017): Vérnyomáscsökkentő gyógyszerterápiák értékének és piaci teljesítményének összehasonlítása. Marketing És Menedzsment 51: Különszám pp. 1-12.

Kovács, B., Simon, J. (2017): The impact of scientific evidence and price level of hypertension drug therapies on their market performance–A Europe based analysis. Vezetéstudomány-Budapest Management Review, 48(5), 49-63.

Kersnik, J, Peklar, J. (2006): Attitudes of Slovene general practitioners towards generic drug prescribing and comparison with international studies. J Clin Pharm Ther. 2006; 31(6):577–83.

Laat, E., Windmeijer, F., Douven, R. (2002): How does pharmaceutical marketing influence doctors' prescribing behaviour? The Hague: CPB.

Lantos, Z., Simon, J., Bacskai, I. (2006): Gyógyszeripari márkázás, Pirulakatedra füzetek

Leeflang, P. S., Wieringa, J. E. (2010): Modeling the effects of pharmaceutical marketing. Marketing Letters, 21(2), 121-133.

Leeflang, P., Wieringa, J. (2009): Modeling the effects of pharmaceutical marketing. Marketing Letters, 21(2), pp.121-133.

Leffler, K. B. (1981): Persuasion or information-the economics of prescription drug advertising. JL & Econ., 24, 45.

Leopold, C., Mantel-Teeuwisse, A. K., Vogler, S., Valkova, S., de Joncheere, K., Leufkens, H. G. M., Wagner, A. K., Ross-Degnan, D., Laing, R. (2014): Effect of the

economic recession on pharmaceutical policy and medicine sales in eight European countries. Bull World Health Organ 92:630–640

Liao, K. H., Ko, B. S., Chen, L. K., Hsiao, F. Y. (2020): Factors Affecting Usage Levels and Trends of Innovative Oncology Drugs Upon and After Reimbursement Under Taiwan National Health Insurance: Interrupted Time Series Analysis. Clin Transl Sci. 2020 Nov;13(6):1288-1297. doi: 10.1111/cts.12829. Epub Jul 16. PMID: 32583962; PMCID: PMC7719368.

Lieb, K., Scheurich, A. (2014): Contact between doctors and the pharmaceutical industry, their perceptions, and the effects on prescribing habits. PloS one, 9(10), e110130. doi:10.1371/journal.pone.0110130

Lionberger, R. A. (2008): FDA Critical Path Initiatives: Opportunities for generic drug development. AAPS J., 10, 103–109.

Lublóy, Á. (2013): Managing the diffusion of pharmaceutical innovations: conclusions from a literature review. Pannon Manag Rev 2:55–85

Lublóy, Á. (2014): Factors affecting the uptake of new medicines: a systematic literature review. BMC Health Serv Res 14:469

Luiza, V. L., Chaves, L. A., Silva, R. M., Emmerick, I. C., Chaves, G. C., Fonseca de Araujo, S. C. et al. Pharmaceutical policies (2015): Effects of cap and co-payment on rational use of medicines. Cochrane Database Syst Rev., Cd007017.

McCarthy, N. (2004): What are CEOs tipping for success? Scrip Magazine, January 10-11

Madahi, A., Sukati, I. (2012): The effect of external factors on purchase intention amongst young generation in Malaysia. Int. Bus. Res., 5, 153–159.

Maggioni, A. P., Van Gool, K., Biondi, N., Urso, R., Klazinga, N., Ferrari, R., Maniadakis, N., Tavazzi, L. (2015): Appropriateness of Prescriptions of Recommended Treatments in Organisation for Economic Co-operation and Development Health Systems: Findings Based on the Long-Term Registry of the European Society of Cardiology on Heart Failure. Value Heal 18:1098–1104

Malhotra, N.K. (2010): Marketing Research, an applied orientation, Pearson, p.929

Mamdani, M., Ching, A., Golden, B., Melo, M., Menzefricke, U. (2008): Challenges to Evidence-Based Prescribing in Clinical Practice. Ann Pharmacother 42:704–707

Manchanda, P., Wittink, D. R., Ching, A., Cleanthous, P., Ding, M., Dong, X. J., Steenburgh, T. (2005): Understanding firm, physician and consumer choice behavior in the pharmaceutical industry. Marketing Letters. 16 (3-4) 293-308.

Mancia, G., De Backer, G., Dominiczak, A., et al (2007): 2007 Guidelines for the Management of Arterial Hypertension. J Hypertens 25:1105–1187

Mancia, G., Fagard, R., Narkiewicz, K., et al (2013): 2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J 34:2159–2219

Medical Online ismeretlen szerző (2010): Tudományos bizonyítékok hierarchiája: http://medicalonline.hu/cikk/5_2__tudomanyos_bizonyitekok_hierarchiaja [Letöltve: 2020.11.08]

Melamed, R. D., Rzhetsky, A. (2018): Patchwork of contrasting medication cultures across the USA. Nat Commun 9, 4022, https://doi.org/10.1038/s41467-018-06205-1

Mizik, N., Jacobson, R. (2004): Are physicians "easy marks"? Quantifying the effects of detailing and sampling on new prescriptions. Management Science. 50 (12) 1704-1715.

Mohsen, A. M., Zurina, M., The Influence of Information, Brand, Medical Representatives and Sales Promotion on Physician Prescribing Decision, Journal of Pharmaceutical Health Services Research, Volume 9, Issue 3, September 2018, Pages 259–269, https://doi.org/10.1111/jphs.12228

Moreno-Torres, I., Puig-Junoy, J., Raya, J. M. (2011): The impact of repeated cost containment policies on pharmaceutical expenditure: experience in Spain. Eur J Health Econ.;12(6):563-73.

Morgan, S. G., Bassett, K. L., Wright, J. M., Evans, R. G., Barer, M. L., Caetano, P. A., Black, C. D. (2005): "Breakthrough" drugs and growth in expenditure on prescription drugs in Canada. BMJ 331:815–816

Mott, D.A., Schommer, J.C., Doucette, W.R., Kreling, D.H. (1998): Agency theory, drug formularies, and drug product selection: Implications for public policy. J. Public Policy Market. 1998, 17, 287–295.

Murshid, M.A., Mohaidin, Z. (2017): Models and theories of prescribing decisions: A review and suggested a new model. Pharm. Pract. 2017, 15, 990.

Murshid, M., Mohaidin Z. (2018): The Influence of Information, Brand, Medical Representatives and Sales Promotion on Physician Prescribing Decision. Journal of Pharmaceutical Health Services Research. 9. 10.1111/jphs.12228.

Muzumdar, J. M., Schommer, J. C., Hadsall, R. S., Huh, J. (2013): Effects of anthropomorphic images and narration styles in promotional messages for generic prescription drugs. Res. Soc. Adm. Pharm., 9, 60–79.

Narayanan, S., Desiraju, R., Chintagunta, P. K. (2004): Return on investment implications for pharmaceutical promotional expenditures: The role of marketing-mix interactions. Journal of marketing. 68 (4) 90-105.

Narayanan, S., Manchanda, P., Chintagunta, P. K. (2005): Temporal differences in the role of marketing communication in new product categories. Journal of Marketing Research, 42(3), 278-290.

Nardi, E. P., Ferraz, M. B. (2016): Perception of the value of generic drugs in São Paulo. Cad. Saúde Pública, 32, 2.

Neslin, S. A., Canadian Association of Medical Publishers (2001): ROI analysis of pharmaceutical promotion (RAPP): an independent study. Canadian Association of Medical Publishers

Newman, C., Ajay, V. S., Srinivas, R., Bhalla, S., Prabhakaran, D., Banerjee, A. (2016): Drugs for cardiovascular disease in India perspectives of pharmaceutical executives and government officials on access and development a qualitative analysis. J. Pharm. Policy Pract., 9, 1–11.

NICE/BHS (2006): Hypertension: management of hypertension in adults in primary care. NICE Clin. Guideline. 34

NICE (2011): Hypertension in adults: diagnosis and management | Guidance and guidelines. In: August 2011, Last Updat. Novemb. 2016. https://www.nice.org.uk/guidance/cg127. [Downloaded: 2018.05.02.]

NICE (2014): Chronic kidney disease in adults: assessment and management | Guidance and guidelines | NICE. In: July 2014, Last Updat. January 2015. https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations#pharmacotherapy. [Downloaded: 2021.05.03.]

Niëns, L. et al. (2010): Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world, PLoS medicine, Vol. 7/8, p. e1000333, http://dx.doi.org/10.1371/journal.pmed.1000333.

Nolte, E., Corbett, J. (2015): International variation in drug usage: an exploratory analysis of the "causes" of variation. Rand Health Q.; 4(4):1.

Nolte, E., Newbould, J., Conklin, A. (2011) International variation in the usage of medicines: a review of the literature. Rand Health Q.; 1(1):4.

Nutescu, E. A., Park, H. Y., Walton, S. M., Blackburn, J. C., Finley, J. M., Lewis, R. K., Schumock, G. T. (2005): Factors that influence prescribing within a therapeutic drug class. J Eval Clin Pract 11:357–365

OECD (2017a) New Health Technologies. OECD. doi: 10.1787/9789264266438-en

OECD (2017b) Pharmaceutical spending. In: OECD data. Paris: OECD Publishing; 2017 (https://data. oecd.org/healthres/pharmaceutical-spending.htm, [Downloaded: 2021.09.03.].

OECD (2020a), OECD Health Statistics (database), https://stats.oecd.org/Index.aspx?ThemeTreeId=9

OECD (2020b), OECD Reviews of Public Health: Latvia: A Healthier Tomorrow, OECD Reviews of Public Health, OECD Publishing, Paris, https://doi.org/10.1787/e9f33098-en.

OECD Data. https://data.oecd.org/. [Downloaded: 2020.12.29.]

O'keefe, D.J. (2002): Persuasion: Theory and Research; SAGE: Thousand Oaks, CA, USA.

Olsson, E., Kalvemark Sporrong, S. (2012): Pharmacists' experiences and attitudes regarding generic drugs and generic substitution: two sides of the coin. Int J Pharm Pract. 2012; 20(6):377–83.

Ong, M., Catalano, R., Hartig T. (2003): A time-series analysis of the effect of increased copayments on the prescription of antidepressants, anxiolytics, and sedatives in Sweden from 1990 to 1999. Clin Ther.; 25(4):1262-75.

Ong, L. M. L., de Heas, J. C. J. M., Hoos, A.M., Lammes, F. B. (1995): Doctor-patient communication: A review of the literature Social Science & Medicine 40(7) pp. 903-918

Orlowski, J. P., Wateska, L. (1992): The effects of pharmaceutical firm enticements on physician prescribing patterns: There's no such thing as a free lunch. Chest. 1992; 102(1):270-3.

Othman N., Vitry, A., Roughead, E. E. (2009): Quality of pharmaceutical advertisements in medical journals: a systematic review. PLoS One 4: e6350

Panteli, D., Arickx, F., Cleemput, I., Dedet, G., Eckhardt, H., Fogarty, E., Gerkens, S., Henschke, C., Hislop, J., Jommi, C., Kaitelidou, D., Kawalec, P., Keskimaki, I., Kroneman, M., Lopez, Bastida, J., Pita Barros, P., Ramsberg, J., Schneider, P., Spillane, S., Vogler, S., Vuorenkoski, L., Wallach Kildemoes, H., Wouters, O., Busse, R. (2016): Pharmaceutical regulation in 15 European countries review. Health Syst Transit. Oct;18(5):1-122. PMID: 27929376.

Paraponaris A., Verger P., Desquins B., Villani P., Bouvenot G., Rochaix L., Gourheux J. C., Moatti J. P., Panel M. G. Paca. (2004): Delivering generics without regulatory incentives? Empirical evidence from French general practitioners about willingness to prescribe in- ternational non-proprietary names. Health Policy. 2004;70(1):23–32.

Peny, J. M. (1994): ACE-inhibitors—an analysis of marketing strategy. Scrip Mag 28:18–21

Petrova, E. (2014) Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development. In: Ding M, Eliashberg J, Stremersch S (eds): Innov. Mark. Pharm. Ind. Emerg. Pract. Res. Policies. Springer New York, New York, NY, pp 19–81

Petty, R.; Cacioppo, J. (1986): The elaboration likelihood model of persuasion. Adv. Exp. Soc. Psychol. 1986, 19, 1–24.

Pharma 14, Global medicine database, Drug database and medicine price index. pharma14.com, [Downloaded 2021.10.06]

Pintz, Gy. (2005): Találd fel magad. Szabadalom, védjegy, oltalom. Akadémiai Kiadó, Budapest, 2005

Polinski, J. M., Maclure, M., Marshall, B., Cassels, A., Agnew-Blais, J., Patrick, A. R., Schneeweiss, S. (2008). Does knowledge of medication prices predict physicians' support for cost effective prescribing policies? The Canadian journal of clinical pharmacology= Journal canadien de pharmacologie clinique, 15(2), e286.

Porter, M. E., Teisberg, E. O. (2006): Redefining health care: creating value-based competition on results. Harvard business press.

Prashanth, D. S., Elias, M. A., Pati, M.K., Praveenkumar, A., Munegovda, C.M., Bhanuprakash, S., Sadhana, S. M., Criel, B., Migdeli, M., Devadasan, N. (2016):

Improving access to medicines for non-communicable diseases in rural India: A mixed methods study protocol using quasi-experimental design. BMC Health Serv. Res., 16, 421.

Prosser, H., Solomon, A., Walley, T. (2003): Influences on GPs' decision to prescribe new drugs-the importance of who says what. Family practice 20 61-68.

Puig-Junoy, J., Rodriguez-Feijoo, S., Gonzalez Lopez-Valcarcel, B., Gomez-Navarro, V. (2016): Impact of the pharmaceutical copayment reform on the use of antidiabetics, antithrombotics and for chronic obstructive airway disease agents, Spain. Rev Esp Salud Publica.;90:E6.

Puig-Junoy, J., Rodriguez-Feijoo, S., Lopez-Valcarcel, B. G. (2014): Paying for formerly free medicines in Spain after 1 year of co-payment: changes in the number of dispensed prescriptions. Appl Health Econ Health Policy.;12(3):279-87.

Quick, J. D., Hogerzeil, H. V., Velásquez, G., Rägo, L. (2002): Twenty-five years of essential medicines. Bull World Health Organ.; 80(11):913-4.

Rácz-Kummer, K. (2009): A gyógyszerpiac szerkezeti sajátosságai. In: 7th Int. Conf. Manag. Enterp. Benchmarking MEB 2009-Proceedings. Budapesti Műszaki Főiskola, Budapest, pp 349–357

Reiffen, D., Ward, M. R. (2005): Generic Drug Industry Dynamics. Rev Econ Stat 87:37–49

Rekettye, G. (2011): Multidimenzionális árazás, Akadémiai Kiadó, Budapest 2011.

Rigby, D. (2010): Collaboration between doctors and pharmacists in the community. Austr. Prescr. 2010, 23, 191–193.

Rizzo, J. A. (1999): Advertising and Competition in the Ethical Pharmaceutical Industry: The Case of Antihypertensive Drugs*. The Journal of Law and Economics, 42(1), 89-116.

Rizzo, J. A., Zeckhauser R. (2009): Generic script share and the price of brand-name drugs: The role of consumer choice. Int. J. Health Care Financ. Econ., 9, 291–316.

Rogers, E. M. (1983): Diffusion of Innovations. Free Press. doi: citeulike-article-id:126680

Rosenthal, M. B., Berndt, E. R., Donohue, J. M., Epstein, A. M., Frank, R. G. (2003): Demand effects of recent changes in prescription drug promotion. In Forum for Health Economics & Policy (Vol. 6, No. 1).

Rothschild, J. M., Lee, T. H., Bae, T., Bates, D. W. (2002): Clinician use of a palm top drug reference guide. J Am Med Inform Assoc 2002;9:223-9.

Rust, R. (1998): What Is the Domain of Service Research? Journal of Service Research, Vol. 1, November, 107.

Sackett, D., Rosenberg, W., Gray, J., Haynes, R., Richardson, W. (1996): Evidence based medicine: what it is and what it isn't. BMJ, 312(7023), pp.71-72.

Salhia, H.O., Ali, A., Rezk, N. L., El Metwally, A. (2015): Perception and attitude of physicians toward local generic medicines in Saudi Arabia: A questionnaire-based study. Saudi Pharm. J., 23, 397–404.

Sanyal, S. N., Datta, S. (2011): The effect of perceived quality on brand equity: An empirical study on generic drugs. Asia Pacific Journal of Marketing and Logistics. 23. 604-625. 10.1108/13555851111183057.

Saposnik, G., Mamdani, M., Terzaghi, M., Saladino, M. L., Silva, B., Tobler, P. N., Caceres, F. (2018): The Role of Prescribing Generic (Non-proprietary) Drugs in the Prevalence of Therapeutic Inertia in Multiple Sclerosis Care. Frontiers in neurology, 9, 835. https://doi.org/10.3389/fneur.2018.00835

Sbarbaro, J. A. (2001): Can we influence prescribing patterns? Clin Infect Dis. 2001; 33(Suppl 3):S240-4.

Scherer, F. M., Ross, D. (1990): Industrial market structure and economic performance. University of Illinois at Urbana-Champaign's Academy for entrepreneurial leadership historical research reference in entrepreneurship.

Scherer, F. M. (2000). The pharmaceutical industry. Handbook of health economics, 1, 1297-1336.

Schumock, G. T., Walton, S. M., Park, H. Y., Nutescu, E. A., Blackburn, J. C., Finley, J. M., Lewis, R. K. (2004): Factors that Influence Prescribing Decisions. Ann Pharmacother 38:557–562

Schwartz, R.K., Soumerai, S.B., Avorn J. (1989): Physician motivations for nonscientific drug prescribing, Soc SciMed, 28, pp. 577-82.

Sewell, K., Andreae, S., Luke, E., Safford, M. M. (2011): Perceptions of and Barriers to Use of Generic Medications in a Rural African American Population, Alabama, Prev. Chronic Dis. 2012, 9, 142.

Shaughnessy, A. F. (2003): STEPS drug updates. Am Fam Physician 2003;68:2342-8.

Sheeran, P. (2002): Intention-behavior relations: a conceptual and empirical review, Eur Rev Soc Psychol, 12, pp. 1-36.

Shekhar, S. K., Jose T. P., Rehin, K.R. (2019): Consumer buying behaviour and attitude towards pharmaceuticals. Int. J. Res. Pharm. Sci., 10, 4.

Shrank, W. H., Liberman, J. N., Fischer, M. A., Girdish, C., Brennan, T. A., Choudhry, N. K. (2011): Physician perceptions about generic drugs. Ann Pharmacother. 2011;45(1):31–8.

Sismondo, S. (2007): Ghost management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry? PLoS Med, 4(9), e286.

Sinnott, S. J., Normand, C., Byrne, S., Woods, N., Whelton, H. (2016): Copayments for prescription medicines on a public health insurance scheme in Ireland. Pharmacoepidemiol Drug Saf.;25(6):695-704.

Sirdeshmukh, D., Singh, J., Sabol, B. (2002): Consumer Trust, Value, and Loyalty in Relational Exchanges. Journal of Marketing, 66(1), 15–37.
http://www.jstor.org/stable/3203367

Skinstad, S. (2012): Norwegian general practitioners' experiences with and attitudes towards generic substitution in pharmacies. Master thesis. University of Oslo; 2012.

Smith, R. D., Correa, C., Oh, C. (2009): Trade, TRIPS, and pharmaceuticals. Lancet, 373, 684–691.

Sorescu, A. B., Chandy, R. K., Prabhu, J. C. (2003): Sources and financial consequences of radical innovation: Insights from pharmaceuticals. J Marketing. 2003; 67(4):82-102.

Spurling, G. K., Mansfield, P. R., Montgomery, B. D., Lexchin, J., Doust, J., Othman, N., Vitry, A. I. (2010): Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Med, 7(10), e1000352.

Steele, M. A., Bess, D. R., Franse, V. L., Graber, S. E. (1989): Cost effectiveness of two interven- tions for reducing outpatient prescribing costs. DICP. 1989; 23:497-500.

Stephan, D., Gaertner, S., Cordeanu, E. M. (2015): A critical appraisal of the guidelines from France, the UK, Europe and the USA for the management of hypertension in adults. Arch Cardiovasc Dis 108:453–459

Stephenson, M. J., Henry, N., Norman, G. R. (1988) Factors influencing antibiotic use in acute respiratory tract infections in family practice, Can Fam Physician, 34, pp. 2149-52.

Straka, R. J., Keohane, D. J., Liu, L. Z. (2017): Potential clinical and economic impact of switching branded medications to generics. Am. J. Ther., 24, 278–289.

Stros, M., Lee, N. (2015): Marketing dimensions in the prescription pharmaceutical industry: a systematic literature review. Journal of Strategic Marketing 23(4) pp. 318-336,

Summary of Commission Decision of 9 July 2014 relating to a proceeding under Articles 101 and 102 of the Treaty on the Functioning of the European Union (Case AT.39612 — Perindopril (Servier)) (notified under document C(2014) 4955) . OJ C 393, 25.10.2016, p. 7–12

Sutton, R.I., Staw, B. M. (1995): What Theory is Not, Administrative Science Quarterly. 40(3) 371-384.

Svensson, S. A., Hedenrud, T. M., Wallerstedt S. M. (2019): Attitudes and behaviour towards psychotropic drug prescribing in Swedish primary care: a questionnaire study. BMC family practice, 20(1), 4. https://doi.org/10.1186/s12875-018-0885-4

Szabóné Streit, M. (1999): Gyógyszermarketing, Medicina könyvkiadó, Budapest

Szarka, E. (1994): Iparjogvédelmi Kézikönyv, Közgazdasági és Jogi Kiadó, Budapest, 1994

Tan, P. N., Steinbach, M., Kumar, V. (2006): Introduction to Data Mining. Pearson Educ. doi: 10.1016/0022-4405(81)90007-8

Theodorou, M., Tsiantou, V., Pavlakis, A., Maniadakis, N., Fragoulakis, V., Pavi, E., Kyriopoulos, J. (2009): Factors Influencing Prescribing Behavior of Physicians in Greece And Cyprus: Results From A Questionnaire Based Survey. BMC Health Serv. Res. 2009, 9, 150.

Thomson, S., Mossialos, E. (2010). Primary care and prescription drugs: coverage, cost-sharing, and financial protection in six European countries. Issue Brief (Commonwealth Fund), 82, 1-14.

Thomson, S., Evetovits, T., Cylus, J. (2017): Financial protection in high-income countries: a comparison of the Czech Republic, Estonia and Latvia. Copenhagen: WHO Regional Office for Europe (http:// www.euro.who.int/en/health-topics/Health-systems/health-systemsfinancing/publications/ clusters/universal-health-coverage-financial-protection) [Downloaded: 2021.08.22.].

Tian, Y., Zhou, H. (2015): From bottom line to consumer's mind: The framing effects of accounting information. Account. Organ. Soc., 43, 56–66.

Toverud, E. L., Hartmann, K., Håkonsen, H. (2015): A Systematic Review of Physicians' and Pharmacists' Perspectives on Generic Drug Use: What are the Global Challenges? Appl Health Econ Health Policy. 2015 Aug.;13 Suppl 1(Suppl 1): S35-45. doi: 10.1007/s40258-014-0145-2. PMID: 25963230; PMCID: PMC4519583.

Tsiantou, V., Zavras, D., Kousoulakou, H., Geitona, M., Kyriopoulos, J. (2009): Generic medicines: Greek physicians' perceptions and pre- scribing practices. J Clin Pharm Ther. 2009; 34(5):547–54.

Tuncay, B., Pagano, S., De Santis, M., Cavallo, P. (2020): Prescribing Behavior of General Practitioners for Generic Drugs. Int J Environ Res Public Health. Aug 14;17(16):5919. doi: 10.3390/ijerph17165919. PMID: 32824051; PMCID: PMC7460010.

Vágási, M., Piskóti, I., Buzás, N. (2006) Innovációmarketing, Akadémia Kiadó, Budapest

Vargo, S. L., Lusch, R. F. (2004): Evolving to a New Dominant Logic for Marketing. Journal of Marketing. Vol. 68, No. 1, 1–17.

Venkataraman, S., Stremersch, S. (2007): The debate on influencing doctors' decisions: are drug characteristics the missing link? Management Science, 53(11), 1688-1701.

Vicciardo, L. J. (1995): The secret weapon in marketing intelligence: Meetings and events analysis is a powerful new tool in researching marketing strategy and success. Med Marketing Media. 1995; 30(Aug):32-6.

Villanueva, P., Peiró, S., Librero, J., Pereiró, I. (2003): Accuracy of pharmaceutical advertisements in medical journals. Lancet 361:27–32/

Virji, A., Britten, N.A. (1991): A Study of the relationship between patients' attitudes and doctors' prescribing, Fam Pract 1991, 8, pp.314-319.

Vogler, S. (2012). The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries–an overview. Generics and Biosimilars Initiative Journal, 1(2), 44-51.

Vogler, S., Österle, A., Mayer, S. (2015). Inequalities in medicine use in Central Eastern Europe: an empirical investigation of socioeconomic determinants in eight countries. International journal for equity in health, 14(1), 1.

Vogler, S., Zimmermann, N. (2016): Glossary of pharmaceutical terms: 2016 update. Vienna: Gesundheit Österreich GmbH; (http://whocc.goeg.at/Publications/Methodology, [Downloaded: 2017.11.06.).

Vogler, S., Gombocz, M., Zimmermann, N. (2017a): Tendering for off-patent outpatient medicines: lessons learned from experiences in Belgium, Denmark and the Netherlands. J Pharm Health Serv Res.;8(3):147–58.

Vogler, S., Paris, V., Ferrario, A., Wirtz, V. J., de Joncheere, K., Schneider, P., Pedersen, H. B., Dedet, G., Babar, Z.-U.-D. (2017b): How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. Appl Health Econ Health Policy 15:307–321

Vrijens, F., Van De Voorde, C., Farfan-Portet M. I., Stichele R. V. (2012): Patient socioeconomic determinants for the choice of the cheapest molecule within a cluster: Evidence from Belgian prescription data. Eur J Heal Econ. doi: 10.1007/s10198-011-0367-2

Wang, C., Li, N., Wang, H., Yin, H., Zhao, Y. (2018): Study on essential drug use status and its influencing factors among cerebral infarction inpatients in county level hospitals of Anhui Province, China. PLoS One. Apr 5;13(4):e0193513. doi: 10.1371/journal.pone.0193513. PMID: 29621245; PMCID: PMC5886397.

Warayuanti, W., Suyanto, A. (2015): The influence of lifestyles and consumers attitudes on product purchasing decision via online shopping in Indonesia. Eur. J. Bus. Manag., 7, 74–80.

Ward, S., Pecotich, A., O'Cass, A., Julian, C. (2008): A Rose by Any Other Name? The Influence of Brand Name versus Chemical Differences in the Prescription of Antidepressants. Journal of Macromarketing, 28 (3), pp.258-274.

Weick, K. E. (1995): What Theory is Not, Theorizing Is, Administrative Science Quarterly. 40(3) 385-390.

Werth, B. (2013): The Billion-dollar Molecule: The Quest for the Perfect Drug. Simon and Schuster.

WHO (2018): Medicines reimbursement policies in Europe.

Willems, S., De Maesschalck, S., Deveugele, M., Derese, A., & De Maeseneer, J. (2005). Socio-economic status of the patient and doctor–patient communication: does it make a difference?. Patient education and counseling, 56(2), 139-146.

Windmeijer, F., De Laat, E., Douven, R., & Mot, E. (2006). Pharmaceutical promotion and GP prescription behaviour. Health economics, 15(1), 5-18.

Winslow, R. (2000): Birth of a blockbuster: Lipitor's unlikely route out of the lab. Wall Street Journal, 24.

World Bank Open Data. https://data.worldbank.org [Downloaded: 2020.12.28.]

Wosinska, M., Huckman R. S. (2004): Generic dispensing and substitution in mail and retail pharmacies. Health Affairs, 23, W4.

Xing, J. L., Othman, M. H. (2015): Rational decision making models might suggest what people ought to do, they are a poor guide to what people actually do. Int. J. Biol. Macromol. 2015, 1, 1–5.

Zerbini, C., Luceri, B., Vergura, D. T. (2017): Leveraging consumer's behaviour to promote generic drugs in Italy. Health Policy. Apr; 121(4): 397-406. doi: 10.1016/j.healthpol.2017.01.008. Epub 2017 Feb 21. PMID: 28233600.

Zwolsman, S., te Pas, E., Hooft, L., Wieringa-de Waard, M., van Dijk, N. (2012): Barriers to GPs' use of evidence-based medicine: a systematic review. Br J Gen Pract 62:511–521

Appendices

Appendix 1 – Detailed analysis of factors influencing diffusion of therapies based on the outcomes of Lublóy's investigated studies (Lublóy, 2014)

Category	Variable	Studies	Effect 1			Effect 2			Significant		Not significant	
			Heading	n	%	Heading	n	%	n	%	n	%
Socio-demographic features	No	15	Women	1	7%	Men	6	40%	7	47%	8	53%
	Age	14	Young	7	50%	Old	2	14%	9	64%	5	36%
	Professional age	5	Negative	2	40%	Positive	2	40%	4	80%	1	20%
	Place of education	5	Overseas (UK, US aspect)	2	40%	Less prestigious, young universities	2	40%	4	80%	1	20%
	Number of current jobs	2	More than one	1	50%	One	0	0%	1	50%	1	50%
Scientific orientation	Specialization	16	Specialists	10	63%	GPs	6	38%	16	100%	0	0%
	Hospital affiliation	8	Hospital environment	2	25%	Office clinical	4	50%	6	75%	2	25%
	Board qualification	6	Board of Directors	2	33%	Other	0	0%	2	33%	4	67%
	Participation in clinical trials	3	Yes	3	100%	No	0	0%	3	100%	0	0%
	CME and pharmacotherapy audit meetings (PTAM)	3	CME	1	33%	Poor-quality PTAM	1	33%	2	67%	1	33%
	Number of professional journals read	3	Positive	2	67%	Negative	0	0%	2	67%	1	33%
	Perceived scientific orientation	3	Professional-oriented	2	67%	Patient-oriented	0	0%	2	67%	1	33%
	Expert meetings and events	3	Positive	3	100%	Negative	0	0%	3	100%	0	0%
	Position	1	Executive	0	0%	Non-executive	1	100%	1	100%	0	0%
Patient's features	Age	9	Young	5	56%	Old	1	11%	6	67%	3	33%
	No	6	Women	0	0%	Men	1	17%	1	17%	5	83%
	Health	4	Yes	3	75%	No	0	0%	3	75%	1	25%
	Socio-economic features	4	High	3	75%	Low	0	0%	3	75%	1	25%
	Marital status	2	Partnership	1	50%	Single	0	0%	1	50%	1	50%
	Ethnicity	2	Non-Afro-American, non-Hispanic	2	100%	Afro-American, Hispanic	0	0%	2	100%	0	0%

Appendix 2: Executive and expert interviews during the exploratory phase of the research

Sándor Héber – Business Analyst, Strategic Marketing and Licensing Department, Gedeon Richter Plc; discussion, March 2016

Tibor Horváth – General Manager, Gedeon Richter Germany (currently: Sales Director, Richter Gedeon Plc.) written interview, May 2016

Dr. Zsolt Szombathelyi – Chief Scientific Officer, Gedeon Richter USA (formerly: Research Director, currently: Advisor to the CEO, Richter Gedeon Plc.) telephone interview, May 2016

Warren Czerniak – President, Gedeon Richter USA; telephone interview, May 2016

Dr. Vera Tóth – Head of Department, Medical Strategy and Coordination, Gedeon Richter Plc; discussion, May 2016

Dear...,

My name is Bence Kovács and I work as a development project manager in the Product Development Department of Richter. Additional to my job, I am a PhD student at the Faculty of Business Administration of Corvinus University. My work so far has been supported by several people from Richter, including Sándor Héber, who suggested that I contact you, so I would like to ask a few questions from you. Your help would mean a lot to me.

In the attached document I have briefly summarised my research concept and results I have achieved so far. (The current results are exploratory.) However, at this point in the research it would be of great help if I could get information from experts with relevant experience in the markets I am studying (USA, Germany, Hungary).

In the attached document, I provide a summary of the concept, an extract of the results so far, an outline of the preliminary conclusions and at the end of the document I have a few questions. I just want to emphasize again that your feedback and answers to these questions would be of great help to me for further defining the focus of my research.

Dear …,

As you might know, beside my life at Richter I am conducting my doctoral research in economics at Corvinus University. As discussed with Warren during his stay in Budapest I would like to turn to you with a few questions concerning my concept. I have compiled a summary in which I explain the basic thoughts about my research. At the end of the document I raise a few questions also. I would be very happy to get feedback from you about your thoughts and recommendations. I perform the analyses with data from the US, Germany and Hungary so your insights into the American market would be very beneficial.

Executive Summary to …

A brief extract of the doctoral research *by Bence Kovács*

The sales and marketing of pharmaceutical products is a highly complex and multifactorial process. In addition to the patient as the final consumer, one should never ignore the prescribing physician and the financing healthcare system, not to mention the regulations and the intertwining of corporate interests and positions. As with other products, the following question arises: What is the basis for selecting the appropriate drug therapy for a given indication? The basic idea of the research is that if an active pharaceutical ingredient (API) can be proved to be better scientifically, then this should have a positive impact on its market performance. Of course, one should make further assumptions. Every compared API should be available in generic form for a relatively long period. The APIs should be comparable, which means that they can be prescribed for treating the same diseases, and we should analyse the prescription drug market. To meet the mentioned assumptions, study of the family of antihypertensive drugs seemed to be an appropriate choice. Amongst the hypertension drugs we can find groups with different methods of action, and several chemical entities within each group. These chemical entities have been available in generic form for a long time and in most of the countries of the world.

Research method

After selecting the antihypertensive drugs as the target pharmaceutical family, the focus of the research had to be approved to groups that are comparable. In order to ensure comparability, we introduced only two groups of antihypertensive drugs with different methods of action, based on data from the literature and interviews with professionals. The two selected groups are:

- angiotensin-converting enzyme (ACE) inhibitors (ATC code: C9A),
- and angiotensin II receptor antagonists (ARBs) (ATC code: C9C).

Based on data from the literature (the conclusions of different medical meta-analyses) and professional interviews, we attempted to define a scientific ranking between and among the groups concerning the APIs' efficacy and safety. It is important to note that we defined the ranks based only on scientific data, but without analysing the market performance of the APIs to any extent, prior to identifying the ranks.

With the scientific ranking in-hand we then executed queries from the IQVIA database to obtain data on the market performance of the different active substances. We collected data on sales volume and sales revenue. We analysed data from the USA, Germany, and Hungary at this stage of the research. To ensure comparability, the database was completed with corresponding defined daily dose (DDD) values for the different substances. We also identified the date of FDA approval for the drugs and the priveo the APIs as indicative data.

To analyse the correlation between the scientific appropriateness and market performance, the scientific ranks were compared with the sales volume. The ratios of sales volumes between the APIs are almost the same as the ratios of the sales volumes normalized with DDD values. For this reason, sales volume can be used directly in the comparison.

The main weakness of the research is that the scientific ranking is hard to defend for the relevant therapeutic group. In spite of this, I strongly believe that this research represents a promising basis that can later be extended to further therapeutic groups whose rankings are more unequivocal.

Results

The recent data are preliminary, and serve only exploratory purposes. The evaluation will be undertaken with more sophisticated methods.

Table M1 and M2: Angiotensin II receptor antagonists (ARBs)

Active Substance	Clinical rank	DDD (mg)	FDA Appro-val	No. of competitors in the USA	No. of competitors in Germany (parallel import incl.)	No. of competitors in Hungary
candesartan	1	8	1998	2	54	2
telmisartan	1	40	1998	2	38	8
irbesartan	2	150	1997	2	38	9
valsartan	2	80	1996	2	31	13
losartan	3	50	1995	2	37	11
olmesartan	3	20	2002	1	15	1
eprosartan	4	600	1997	2	14	1

Active Substance	Clinical rank	Sales Volume in the USA CU MAT/9/15 (%)	Sales Volume in Germany CU MAT/9/15 (%)	Sales Volume in Hungary CU MAT/9/15 (%)
candesartan	1	1,3	43,4	3,0
telmisartan	1	2,5	7,2	18,7
Irbesartan	2	6,0	5,6	11,5
Valsartan	2	16,1	31,1	40,4
Losartan	3	66,8	10,0	26,4
olmesartan	3	7,0	1,8	0,0
eprosartan	4	0,0	0,6	0,0
ARB / ARB+ACE (%)	-	**31,0**	**32,6**	**29,2**

Table M3 and M4: Angiotensin-converting enzyme (ACE) inhibitors

Active Substance	Clinical rank	DDD (mg)	FDA Appro-val	No. of competitors in the USA	No. of competitors in Germany (parallel import incl.)	No. of competitors in Hungary
ramipril	1	2,5	1991	2	28	15
enalapril	2	10	1985	3	31	9
fosinopril	2	15	1991	2	4	3
Lisinopril	2	10	1987	3	27	4
perindopril	2	4	1993	2	3	17
captopril	3	50	1981	2	27	2
trandolapril	4	2	1996	2	1	3
quinapril	5	15	1991	2	4	1
benazepril	5	7,5	1991	2	5	1

Active Substance	Clinical rank	Sales Volume in the USA CU MAT/9/15 (%)	Sales Volume in Germany CU MAT/9/15 (%)	Sales Volume in Hungary CU MAT/9/15 (%)
ramipril	1	5,8	72,1	33,0
enalapril	2	8,5	15,9	17,3
fosinopril	2	1,0	0,2	1,9
lisinopril	2	74,6	9,0	3,3
perindopril	2	0,1	0,1	37,1
captopril	3	0,8	1,9	5,7
trandolapril	4	0,3	0,0	0,3
quinapril	5	2,7	0,3	1,2
benazepril	5	6,1	0,4	0,2
ACE / ARB+ACE (%)	-	**69,0**	**67,4**	**70,8**

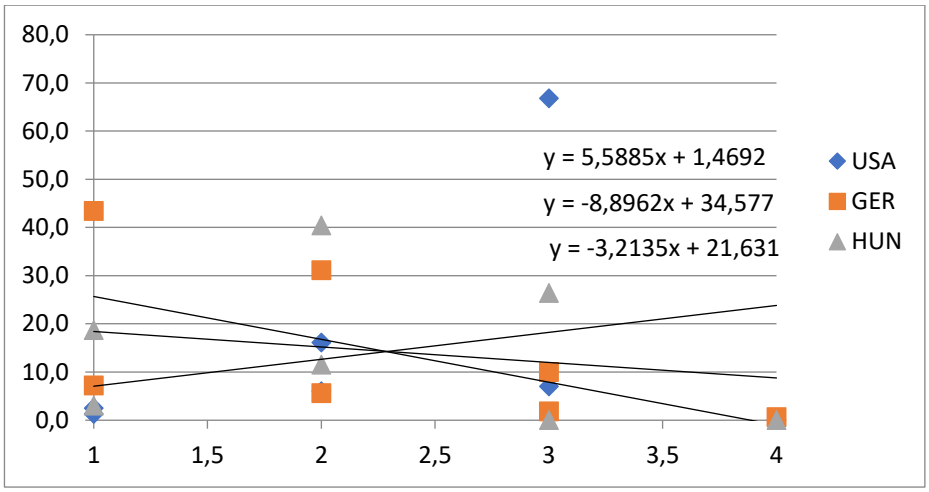


Diagram M1.: Sales ratio of Angiotensin II receptor antagonists (ARBs) as a function of clinical rank

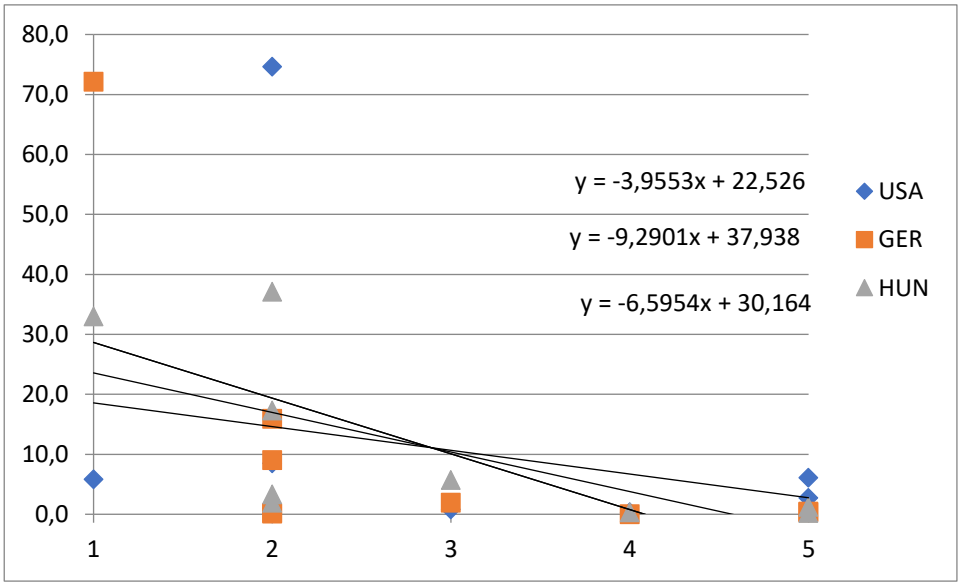


Diagram M2.: Sales ratio of Angiotensin-converting enzyme (ACE) inhibitors as a function of clinical rank

Conclusions

As I have mentioned above, the results are still preliminary but demonstrate interesting relationships:

- The distribution of sales ratios between the two groups is similar in the different countries: ACE:ARB=30:70. Although the ARBs are considered to be better scientifically (with regard to safety), the lower price level of ACE inhibitors can explain this phenomenon.
- More competitors leads to better correlation between the clinical rank and the market performance. In Germany (described by a high level of generic competition) most sales are generated by the API with the lowest clinical rank.
- The previous statement is only weakly true concerning Hungary (no correlation in the group of ARBs), where the level of competition is lower.
- Considering the data from the US, we find weak correlation in the group of ACE inhibitors, and there is no correlation in the group of ARBs. The level of competition is the lowest in the USA.
- The price level for daily therapy within ARBs and ACE inhibitors:
    - ARBs: the price levels are comparable, except for telmisartan, whose price is higher.
    - ACE inhibitors: the price levels are comparable, except for fosinopril, quinapril, trandolapril and benazepril, with higher price levels.

Questions

With the preliminary results in my hand, your professional insights would strongly support and help refine my further research goals. For this reason, your feedback would be greatly appreciated in relation to the subsequent questions:

- Please share your thoughts about the research concept in general.
- Do you think that there is a positive correlation between the clinical rank of a drug and its market performance in general? Please explain your answer. To what extent is this statement true considering your country?
- Do you think that an increase in the level of competition can positively and strongly affect the above-described positive correlation? (The authors have a hypothetical explanation for this, but would greatly appreciate your thoughts on the topic too)
- Do you think that the column ‘number of competitors’ from the IQVIA database for your country can be considered valid?
- How would you interpret the preliminary results. Did the results surprise you?
- What are the main factors in your country that can explain the results?
- How would you refine the analysis?

- Which therapeutic group(s) would you consider involving in such research?
- What other factors influence the correlation between the clinical ranks and the market performance?

Appendix 3: Interview guidelines – third phase of the research

Dr. Hajnalka Minda – Head of International Marketing Department (Interview 1)
Richter Gedeon Plc, Budapest, 11 a.m. 21 March 2019

Interview questions:

- Would you please describe briefly your work in this department at Richter? How is the market working, and what steps do you take to ensure the successful operation of the company?

Research questions:

Product branding

- Talking about market entry, which element of the 4Ps—from a marketing perspective—is the most pronounced one? Can you rank the 4P?
- What marketing strategy does Richter employ to maximize the sales of the product group I have described?
- Is the marketing strategy of your competitors different? If yes, how so?
- Is there any difference between the branding strategy of the HQ and that of the subsidiaries?
    - If they are different, does this pose any difficulty with the global brand identity?
- What considerations are taken into account and what analyses are done to help decide whether a product/product line will be lunched into the market as **branded** or **non-branded**?
- At Richter, what is the **distribution** of branded and non-branded products?
    - Looking at the European countries, is there any change in the distribution of branded and non-branded products?
- Looking at **brand building** for generic prescription-only products, what are the most important aspects that must be addressed, and **characteristics to be developed?**
    - To what extent do you see that **physicians' perception can be influenced,** and is there any difference between countries?
    - Considering drug choice, what do you think are the **most significant influencing factors**? Could you rank them?
- When you look at countries individually, are there any changes in terms of **product branding?** If so, what are they, specifically in relation to **ACE, ARB inhibitors?**

- Are sales representatives of Richter promoting ACE/ARB inhibitors as a single product or as a product line? If the latter, as multiple products at one time, what place do ACE/ARB inhibitors occupy in the product line?
- How are the **principles of evidence-based medicine** considered at Richter when **marketing decisions** are made?
- How does marketing and **product branding change** along the product life cycle? How often do you review your product marketing? If it changes, how does it change (e.g., priority order of 4P changes, less emphasis on promotion)?

Country-of-origin effect

- Is there any survey or study on drug choice that explores the **positive** (negative) **country-of-origin** effects of the company? If you are aware of the effect, how do you intend to reinforce it (in positive cases)?

➢ Who else do you think should be interviewed about this subject?

➢ In your opinion, is there any important factor that has not been mentioned in the interview, but would be worth considering?

➢ What is your opinion of the research methodology?

Dr. Templomné dr. Beatrix Rausch – Head of Cardiology Marketing Department, and
Dr. Ágnes Hidász – Cardiology Marketing Department, Product Manager (Interview 2)
Richter Gedeon Plc, Budapest, 2 p.m. 21 March 2019

Interview questions:

- Would you please briefly describe your work in this department at Richter? How is the market working, and what steps do you take to ensure the successful operation of the company?

<u>Research questions:</u>

Product branding

- Talking about market entry, which element of the 4Ps—from marketing perspective—is the most pronounced one? Can you rank the 4P?
- What marketing strategy does Richter employ to maximize the sales of the product group I have described?
- Is the marketing strategy of your competitors different? If yes, how so?
- Is there any difference between the branding strategy of the HQ and that of the subsidiaries?
    - If they are different, does this pose any difficulty with the global brand identity?
- What considerations are taken into account, and what analyses are done to help decide whether a product/product line will be lunched into the market **branded** or **non-branded**?
- At Richter, what is the **distribution** between branded and non-branded products?

        - Looking at the European countries, is there any change in the distribution of branded and non-branded products?
    - Looking at **brand building** for generic prescription-only products, what are the most important aspects that must be addressed, and **characteristics to be developed?**
        - To what extent do you see that **physicians' perceptions can be influenced,** and is there any difference between countries?
        - Considering drug choice, what do you think are the **most significant influencing factors**? Could you rank them?
    - Are there any changes in terms of **product branding** when looking at country by country? If so, what are they, specifically for **ACE, ARB inhibitors?**
    - Are sales representatives of Richter promoting ACE/ARB inhibitors as a single product or as a product line? If the latter, as multiple products at one time, what place do ACE/ARB inhibitors occupy in the product line?
    - How are the **principles of evidence-based medicine** considered at Richter when **marketing decisions** are made?
    - How does marketing and **product branding change** along the product life cycle? How often do you review your product marketing? If it changes, how does it change (e.g., priority order of 4P changes, less emphasis on promotion)?

Country-of-origin effect

- Is there any survey or study on drug choice that explores the **positive** (negative) **country-of-origin** effects of the company? If you are aware of the effect, how do you intend to reinforce it (in positive cases)?
-

- Who else do you think should be interviewed about this subject?
- In your opinion, is there any important factor that has not been mentioned in the interview, but would be worth considering?
- What is your opinion of the research methodology?

Zsolt Safranka, International Sales Department, Head of International Network of Sales Representatives (Interview 3)

Richter Gedeon Plc, Budapest, 10 a.m. 22 March 2019

Interview questions:

- Would you please briefly describe your work in this department at Richter? How is the market working, and what steps do you take to ensure the successful operation of the company?

<u>Research questions:</u>

- What are the roles and responsibilities of a sales representative?
- How do you analyse and evaluate the work of sales representatives?

Country-of-origin effect

- Is there any survey or study on drug choice that explores the **positive** (negative) **country-of-origin** effects of the company? If you are aware of the effect, how do you intend to reinforce it (in positive cases)?
-

- Who else do you think should be interviewed about this subject?
- In your opinion, is there any important factor that has not been mentioned in the interview, but would be worth considering?
- What is your opinion of the research methodology?

Annex 4 – Statistics from the factor analysis

	Professional type of marketing	Marketing communication, professional,	External reinforcement	Regulations	Branding elements	Hungary	Total
Variance explained	12.69%	12.42%	11.18%	10.04%	9.40%	8.49%	64.22%
Cronbach Alfa	0.837	0.839	0.799	0.726	0.794	0.882	**Communality**
18. Education, training programmes sponsored by pharmaceutical companies	0.837	0.242	-0.075	0.039	0.144	0.048	0.788
16. Research support provided by pharmaceutical companies	0.829	0.124	-0.083	0.065	0.103	0.106	0.736
19. Pharmaceutical industry presence at professional events	0.711	0.117	0.030	0.165	0.199	0.175	0.617
15. Drug samples provided by pharmaceutical companies	0.693	0.061	0.126	0.134	-0.003	0.053	0.521
31. Expertise of sales representatives	0.113	0.854	0.029	-0.026	0.183	0.051	0.780
30. Good relationship between physicians and sales representatives	0.228	0.811	-0.037	-0.189	0.289	-0.043	0.832
32. Stability of the pharmaceutical company (history)	0.054	0.621	0.112	0.116	0.230	0.509	0.727
11. Information received from pharmaceutical companies during drug detailing	0.358	0.603	0.210	0.100	-0.098	0.077	0.561
28. Form of financing for a particular therapy	-0.100	0.569	-0.052	0.390	0.223	0.179	0.570
29. Recommendations from recognized physicians, opinion leaders	0.284	0.561	0.279	0.306	0.023	0.323	0.672
8. Ease of administration, expected patient compliance	-0.281	0.058	0.717	0.126	0.101	0.014	0.623
5. Costs or cost level of the therapy relative to other therapies	-0.086	0.085	0.679	-0.034	0.041	-0.017	0.479
12. Information received from pharmaceutical companies during online detailing	0.248	0.071	0.609	0.089	0.218	0.197	0.532
7. Opinions and recommendations of clinical pharmacists	0.140	-0.083	0.588	0.299	0.040	0.274	0.538
23. Patients' requests for prescribing therapies	-0.006	-0.012	0.531	-0.024	0.412	0.155	0.477
13. Opinions and recommendations from peers	0.342	0.265	0.520	0.212	0.075	-0.196	0.547

20. Advertisements in professional journals (paper and online)	0.450	0.020	0.484	0.211	0.361	0.324	0.717
14. Information about hospital prescribing practices	0.347	0.398	0.432	0.267	-0.170	0.113	0.578
6. Available guidelines for prescribing	0.140	0.084	0.139	0.761	-0.057	0.105	0.639
2. Number of authorized indications for drug therapy	0.005	-0.133	0.134	0.760	0.171	-0.008	0.642
10. Availability of written professional information about the therapy, professional content	0.094	0.081	0.289	0.689	-0.050	0.106	0.588
4. Therapy-related prescribing restrictions	0.169	0.134	-0.115	0.632	0.052	0.017	0.462
26. Visual appearance and packaging of drugs	0.041	0.125	0.160	0.119	0.800	0.303	0.789
22. Small gifts from pharmaceutical companies (pens, etc.)	0.336	0.164	0.120	-0.097	0.745	0.077	0.724
27. Slogans of pharmaceutical companies, brand associations	0.054	0.387	0.162	0.104	0.666	0.307	0.728
21. Quality of materials from sales representatives	0.242	0.271	0.263	0.323	0.412	-0.082	0.482
33. Drugs are produced in Hungary	0.141	0.196	0.081	0.064	0.193	0.859	0.843
24. Drugs were developed in Hungary	0.181	0.086	0.146	0.083	0.225	0.819	0.790

Annex 5 – Normality tests for clusters

Table M5a. Significance values of normality tests for the frequency of prescribing APIs in the five clusters

Cluster	df	ramipril	enalapril	fosinopril	lisinopril	perindopril	captopril	trandolapril	quinapril	benazepril
Fully informed	35	0.124	0.002	<0.001	0.001	0.200	<0.001	<0.001	<0.001	<0.001
Bureaucrats	61	0.008	<0.001	<0.001	<0.001	0.200	<0.001	<0.001	<0.001	<0.001
Sensitive to brands and country of origin	33	0.022	<0.001	<0.001	0.005	0.200	0.001	<0.001	<0.001	<0.001
Efficiency seekers	19	0.200	<0.001	<0.001	0.004	0.088	0.088	<0.001	<0.001	<0.001
Sensitive to drug detailing	7	0.050	0.063	<0.001	0.002	0.200	0.107	NA	NA	NA

Table M5b. Significance values of normality tests for the frequency of prescribing APIs in the five clusters

Cluster	df	candesartan	telmisartan	irbesartan	valsartan	losartan	olmesartan	eprosartan
Fully informed	35	<0.001	0.106	0.006	0.200	0.001	<0.001	<0.001
Bureaucrats	61	<0.001	0.010	0.003	0.200	<0.001	<0.001	<0.001
Sensitive to brands and country of origin	33	<0.001	0.102	0.120	0.200	0.029	<0.001	<0.001
Efficiency seekers	19	<0.001	0.200	0.196	0.200	0.022	<0.001	<0.001
Sensitive to drug detailing	7	0.007	0.200	0.083	0.170	<0.001	NA	NA

Table M5c. Significance values of normality tests for prescribing habits and attribute ranks in the five clusters (Normality was not assumed in any cluster for the category 'Other')

Cluster	df	When you prescribe a drug, do you prefer to make your decision about a particular brand or a particular API?	Regulatory, institutional guidelines, protocols	Studies	Scientific medical literature	Scientific journals	Information from sales representatives	Peers' experiences, recommendations	Internet resources
Fully informed	35	0.002	<0.001	<0.001	<0.001	0.002	0.001	0.019	<0.001
Bureaucrats	61	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sensitive to brands and country of origin	33	<0.001	<0.001	<0.001	0.003	0.003	<0.001	<0.001	<0.001
Efficiency seekers	19	0.021	<0.001	<0.001	<0.001	0.002	0.085	0.159	<0.001
Sensitive to drug detailing	7	<0.001	0.007	NA	0.200	0.031	0.140	0.063	NA

Annex 6 – Details of physicians participating in the selection of drug therapies

Dr. István Kovács PhD, Surgeon, Bugát Pál Hospital, Gyöngyös; discussion, November 2015

Dr. Vera Tóth, Head of Department, Medical Strategy and Coordination, Gedeon Richter Plc; discussion, May