CORVINUS UNIVERSITY of BUDAPEST

Doctoral School of Business and Management

SUMMARY OF THESES

Bence Kovács

The path from clinical evidence to use of drugs

Marketing analysis of factors influencing the market performance of drug therapies

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Supervisor:

Dr Judit Simon

Co-Supervisor:

Dr. Ildikó Kemény

Budapest, 2022.

Institute of Marketing

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Contents

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

In my research, I sought to answer the following questions:

- To what extent does clinical evidence determine the extent of drug use? In other words, regarding therapies that are made available to patients, are they the clinically most appropriate ones?
- 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 above questions?

My research is based on the Maxwell model, illustrated in figure 1. My initial assumption is that, in ideal circumstances, the prescription and hence sales of active ingredients (APIs) are defined according to the clinical appropriateness of therapies. During both the secondary research and the expert interviews, this factor was the focus, and the aim of the literature review was also to explore the importance of clinical appropriateness and how it is reflected in drug sales.

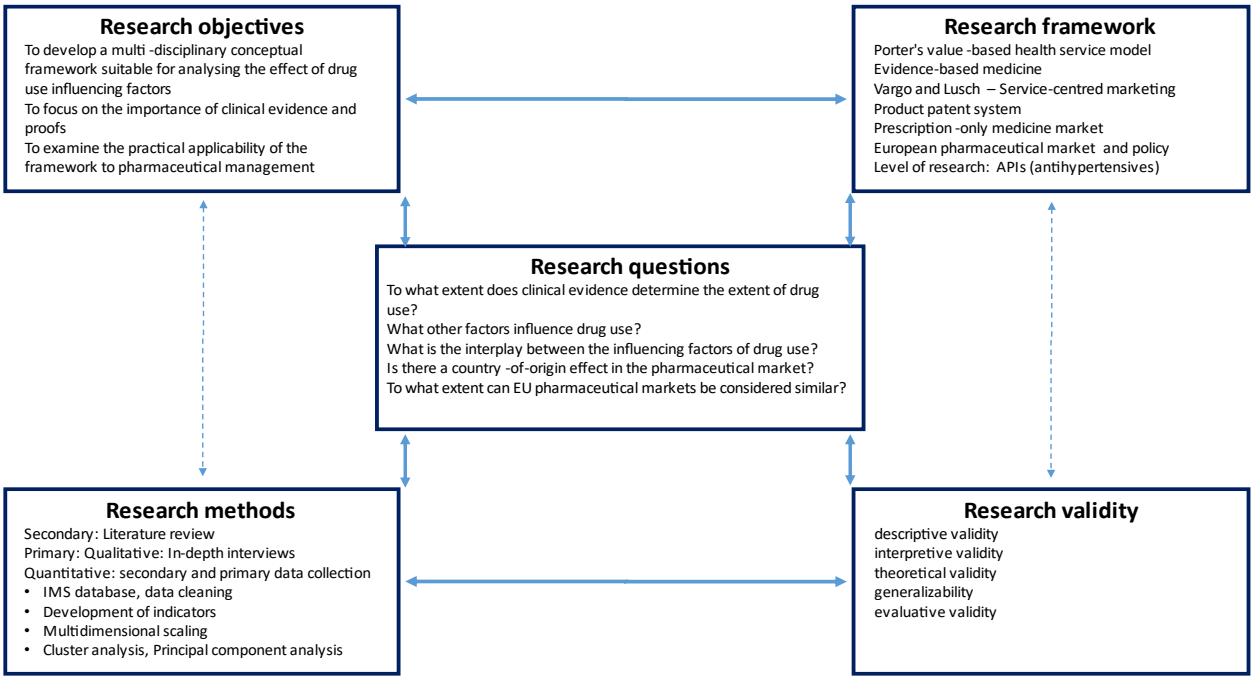

Figure 1. Definition of the field of research according to Maxwell's research model

The literature review in the thesis includes an analysis of the pharmaceutical market, followed by a summary of the available knowledge about the factors that determine the prescribing and sales processes, highlighting the impact of clinical appropriateness, physician perception, pharmaceutical marketing activities, and pharmaceutical policy instruments. I consider the main value of the doctoral research to be that no comprehensive work can be found that provides a theoretical framework concerning how the impact of clinical appropriateness is communicated to the patient in respect of the complex interrelationships associated with the pharmaceutical market, and there is no literature that provides guidance on how this can be researched coherently.

2. Research methodology

The aim of the first phase of my research was to explore possibilities and to fill up Maxwell's dimensions with content that are relevant to my research. In doing so, the field of my research was able to 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. Essentially, 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 was linked to the previous one (what other factors might distort this relationship), and after that came another question – how might this be investigated and generalized in a methodologically adequate way? The first stage of exploring possibilities was marked by qualitative research, including expert interviews, in parallel with a literature review. Expert interviews with physicians confirmed the choice and the ranking of therapeutic classes; then, with the use of qualitative methods the context of the relationships was explored and constructed to explain the interplay between clinical appropriateness and market performance in drug purchasing decisions. This framework also formed the basis for my marketing research. The qualitative research was complemented with a quantitative analysis, the objective of which was twofold. On the one hand, I wanted to understand as thoroughly as possible the specific market patterns and interpret them within the framework that was constructed according to the qualitative research. To do this, I saw the need for both cross-sectional and a longitudinal studies, focusing on nine European pharmaceutical markets. On the other hand, I wanted to quantify the impact of the factors that exert a profound influence on drug prescription. To meet the first objective, secondary data were analysed, and to satisfy the second objective, primary marketing research was carried out.

2.1. Qualitative research methodology. An analysis of factors influencing market performance

2.1.1. The second and third phase of qualitative research: the 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 the research framework defined up to that point. Experts were selected through snowball sampling. In the first round—which was the second phase of my research—I consulted with colleagues working in strategic marketing and then, in consultation with them, additional interviewees were selected.

In the third phase of research, I focused on the main determinants of drug prescription, highlighting 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 that had emerged during the expert interviews. Once the concepts were clarified, I tried to make connections between the category and its dimensions. All along, I was careful not to lose focus on the interplay between clinical evidence and market performance. The main difficulty was ensuring that the research framework was not distorted during the interviews, partly by 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.

2.1.2. The fourth phase of qualitative research: framework finalization

The continuous development of the 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 seemed to become clear. Factors that determine the relationship between clinical evidence and market performance were arranged into a logical chain, and re-reading the interview drafts a new system of codes emerged. In the results chapter of the dissertation, I attempted to draw conclusions from the primary research results and reinterpret the codes to present a theoretical structure of the studied relational system.

2.2. Quantitative research methodology

In the doctoral research, two types of analysis were conducted based on secondary data and a primary marketing research was also performed. On the one hand, two effect classes (ARB vs ACE) were compared, and on the other, the active ingredients of ACE inhibitors were also compared based on sales volumes and sales revenues for each country. 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. Following this, research into ACE inhibitors was extended to analyse data from 2018 and 2021. Quantitative research was complemented with an additional marketing survey, one aim of which was to compare physicians' and sales representatives' preferences, while another was to explore which factors affect, and to what extent, physicians' drug-prescribing choices.

2.2.1. Market data used for the analysis

For the analyses, data were derived from two sources:

- Secondary information about market performance was obtained from the IQVIA Health MIDAS database. At the first level of research, distribution by pharmaceutical form was investigated filtered by *per os* pharmaceutical form. The analysis covered nine countries (France, Germany, Hungary, United Kingdom, Spain, Italy, Poland, Romania, and the Netherlands). A methodological suggestion was developed to ensure the comparability of sales data across countries and drug therapies.
- The primary dataset of marketing research was based on a questionnaire survey with 261 participants (155 physicians and 106 sales representatives).

2.2.2. Quantitative research methodology

Secondary data (IQVIA) were analysed using multidimensional scaling (to help visualise similarities and differences across countries) and cluster analysis (to group active ingredients) to detect similarities and differences between active ingredients and countries. To do this, country sales data were used to explore market performance and its patterns. The analysis was further enriched by the visualization of time-series data, while a custom indexing methodology was developed for data interpretation and comparison, and a market concentration index was also used. The derived indicators were as follows: Price level of ARB and ACE inhibitors, price level difference index (ratio of ARB price level to ACEI price level), volume difference index (ratio of ARB volume to ACEI volume), sales revenue index (ratio of ARB sales revenue to

ACEI sales revenue), and ARB preference index. In addition to the derived indices, the market concentration was described according to Hirschman's concentration index (HHI).

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

The methodology that was used to analyse the database generated in the framework of primary research was based on an independent samples t-test (comparing physicians' and sales representatives' preferences), factor analysis (categorising the factors influencing physicians' prescribing choice of active ingredients into dimensions) and cluster analysis (using the dimensions generated in the factor analysis to classify respondents into clusters). Clusters were compared using ANOVA or the Kruskal-Wallis test, depending on whether the conditions were met.

In the thesis, secondary data and marketing research results were interpreted in relation to each other. Data were processed using Microsoft Excel 2010, Stata IC 13.1, and SPSS Statistics 25.0 software.

3. Results of the thesis

3.1. Results of the qualitative research

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

Research into prescription-only drugs revealed that prescribing physicians are the most important players in the context of relationships. Clinical literature is one of the most important sources of their knowledge, and physicians acquire and gain insight during their studies and their practice.

The primary aim of pharmaceutical industry players is to make a profit while meeting patients' needs. 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 perspective of originator sales). Through their marketing efforts (detailing, PR, conferences, trade journals), pharmaceutical companies supply prescribing physicians with an increasing amount of information, attempting 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 providing 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 practice of ghost-writing, including scientific articles ostensibly written by independent authors which in fact are supported by pharmaceutical companies. 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' ones. An important role is played by the therapeutic guidelines (professional aspects) on which medication is based in each country, and by what other principles are considered in regulation (e.g., price). One anomaly is that in certain markets companies can shift these factors when their capital strength or marketing potential is large enough to do so. On the whole, in their marketing efforts pharmaceutical companies tend to focus on how to allocate marketing expenditure across marketing activities directed towards physicians, patients, financiers, and pharmacies.

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 through the cost-benefit analysis of the therapy, and as for generic authorization, the quality and clinical equivalence of the originator product has to be assured. In most parts of the developed world, drug prices are reimbursed by the state, particularly in European pharmaceutical markets, and for the subject of the analysis, also for hypertension therapies. 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 actually the retail price reduced by the level of reimbursement. The amount paid out as reimbursement makes public authorities, as financiers, important shareholders in the context of relationships. At this point, public regulation comes back into play as an important factor, in this context as an instrument of pharmaceutical policy. Here, it is worth mentioning that an authoritative factor is the professional and institutional guidelines that play a very important role in prescribing drugs, also through physicians.

The whole set of relationships concerns patients, as the key question is whether patients are receiving the right therapy, yet they do not play a central role in the framework under

consideration. One reason for this – the main one –is that most patients do not have the knowledge to objectively evaluate the value of therapies. However, there is a trend for patients to be increasingly informed in their efforts to influence physicians' decisions. Information is mostly gathered from the internet or from patients' environment. Patients also make a financial decision when buying drugs, so the price to be paid is also an influencing factor.

The distribution network is of less importance in the interplay between clinical appropriateness and market potential. Wholesalers exert their effects mainly indirectly (parallel imports, persuasion of retailers) but retailers must be considered in the equation. Although the extent varies from country to country, pharmacies can influence purchasing decisions. 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 another issue that should not be ignored. Since generic drug therapies are examined at the API level, the reason why this is important is that the number of pharmaceutical companies that launch 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, considering the correlation at the level of the active substance.

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

Physicians are subject to a myriad of influencing factors, the strength of which is controversial.

For generic products, two types of marketing communication are distinguished, with varying degrees of activity. According to one type, brand building is not a common activity; manufacturers typically give discounts to retailers and pharmacists, using non-proprietary names (INN) for drugs, so due to higher margins pharmacists will offer the drugs that bring more benefit to them. When appropriate, they 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.

A good relationship between physicians and pharmaceutical companies is the most important factor, in which sales representatives play a crucial role, and whose work and performance can have enormous influence on the market performance of a product. During drug detailing three main issues should be considered: the frequency of visits, the quality of visits, and sales representatives' commitment and motivation. Other important marketing features include the form of the drug, how patients take the medicine, and branding (slogan associated with the product, the shape and font of the logo, the colours of the product, the packaging, the size of the pack and the product, etc.), as differentiation is essential.

To develop a good professional relationship with physicians, the pharmaceutical industry sponsors congresses, conferences, professional training programmes and other social events for physicians. In developing a price strategy, manufacturers aim to maintain the widest possible patient care while complying with the law and optimizing patient access to drugs – and in addition to that, striving to associate added value to their products. Interviews resulted in contradictory opinions regarding the country-of-origin effect; some respondents were of the view that local producers were preferred, while others thought that there was no preference for local producers.

The main aim of each marketing action is to have the company's products accepted into the evoked set of physicians when they decide about which drug to prescribe. The period under review is characterised by the tightening of regulation concerning pharmaceutical marketing activities in Europe.

3.1.3. Complex set of relationships between the main determinants of drug use

Based on the qualitative research results, a framework was constructed (see Figure 2). For my doctoral research, creating a framework is a major achievement, with the help of which I aimed 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 a marketing approach.

The coding of levels, a hitherto unexplored element, involves at which level each factor exerts its effect (API/brand/mixed); furthermore, what interests are behind the effects (API/brand/mixed) and what the direction of the effects is (enhancing, distorting, or neutralizing the impact of clinical evidence). Results revealed that clinical appropriateness plays a role almost without exception in all factors that determine sales at the API level, but it

is certainly not the sole and may not even be the dominant factor in the complex set of interrelationships involved in purchasing decisions associated with the pharmaceutical industry.

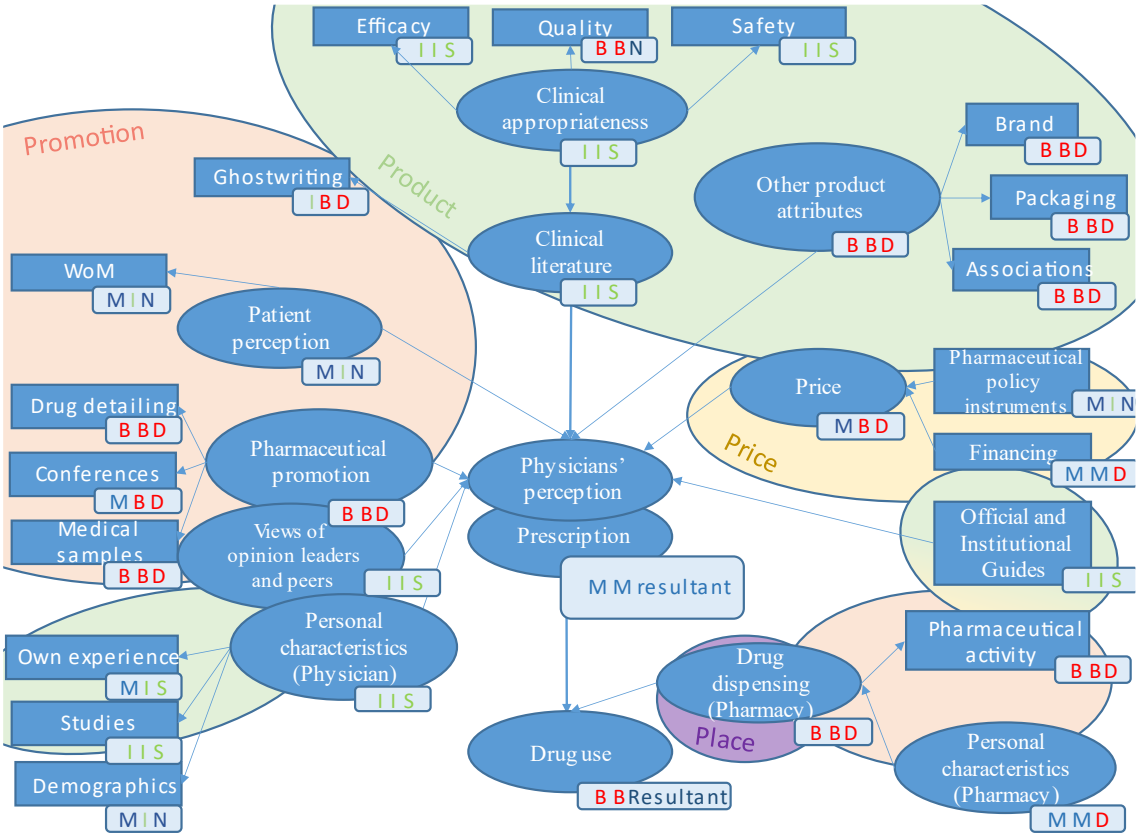

Figure 2. Complex set of relationships between the main factors influencing drug use and the impact of clinical appropriateness on each factor (explanation for the level of impact, the underlying interest, and the direction of the impact)

Since the conditions for perfect competition are far from in place (because of the limited number of competitors due to barriers to entry, and imperfect information supply), physicians' perceptions of clinical appropriateness, the resulting prescriptions, 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 this 'noise' and can only be seen in the anomalous sales figures.

The figure attempts to illustrate the large number of factors that influence drug-prescribing decisions, dispensing and consumption. The impact of clinical appropriateness, a key product attribute, prevails to a different extent in the framework. The letters next to each factor specify responses to the following questions:

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 is investigated in the marketing mix. The figure shows that, apart from clinical appropriateness at the API level, the other product attributes—which can be interpreted at the brand level—have potentially distorting power. From a marketing perspective, these are the factors through which market players can exert the greatest influence on the sales of their own products through their marketing efforts. The figure is not intended to suggest that pharmaceutical and retail actors with business interests only have a negative effect on the relationships, but I think it is important to highlight that the business and economic interests both of public and business players can influence the use of drugs if based on clinical data alone. An awareness of the factors included in the framework of the qualitative research and their interaction creates the basis for an in-depth analysis of the quantitative research results and deeper 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 for the interaction of business, social, and professional interests.

3.2.Results of the quantitative research

3.2.1. Results of the analysis in 2016

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

Clinical studies have proved that ARB therapies are considered clinically more beneficial than ACE inhibitors. Multidimensional scaling can be used to properly examine how similar the nine European countries are in terms of market data for ACE and ARB therapies. The first dimension of the model 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.

The UK is the only country that is difficult to classify into one of the four groups, because it has a relatively small market share of ARBs, but this is achieved at a higher price level. Figure 3 illustrates that the Spanish market is ranked first, with a high sales volume of ARBs (41.91%) even at an exceptionally high price level. The French and Italian pair form a group with similar

ACE-ARB price level and large shares of ARBs. The Dutch market can be considered average in all respects, but with a larger-than-average ARB share it is more similar to the previous group. The German market, although underperforming in terms of ARB volume, achieves this at a high price level. The last group is made up of the Hungarian, Romanian, and Polish markets, where the price level is close to that of ACE inhibitors, combined with a small ARB share.

Figure 3. Results of multidimensional scaling

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

Of the two therapeutic classes, ACE inhibitor therapies were also analysed at API level. The analysis of ACE inhibitors revealed that within the therapeutic class the sales of four compounds are most significant. A ramipril, enalapril, lisinopril and perindopril accounted for a large share of sales (76.6 - 98.8 %) in the studied countries. In general, these APIs have a high clinical ranking (first and second) of all ACE inhibitors, but the share varies among 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). Further, fairly high sales figures were also achieved in Hungary (33% share). The market share is modest in Spain (17.6%) and Romania (18.5%), while the Netherlands (5.4%) is lagging behind in this regard.

The data were again further analysed using multidimensional scaling to compare the consumption patterns of 11 different ACE inhibitors across the nine European countries. The following country groups can be distinguished:

- DE, IT, UK, PL: Countries with the best market performance of the highly recommended ramipril according to clinical appropriateness. Germany is the country closest to the ideal market in terms of the consumption of ACE inhibitors.
- FR, HU: These countries are dominated by use of 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.
- RO, NL: 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.
- ES: The Spanish ACE inhibitor market is clearly dominated by enalapril, with ramipril also accounting for significant sales.

The raw sales data on ACE inhibitors were also analysed in the European countries through subjecting the dataset to ALSCAL multidimensional scaling, and then cluster analysis. Both the MDS and the cluster analysis produced very similar results. The four distinguishing clusters are the following:

- A class of APIs with very small sales volumes in the studied countries: benazepril, trandolapril, fosinopril, quinapril, captopril and zofenopril.
- Lisinopril and perindopril.
- Enalapril.
- Ramipril.

The results show that ramipril is the real leader in Europe, accounting for the highest sales in Germany, Italy, France, UK and Poland, and significant sales in all other countries except for in the Netherlands. As for the results from the patients' perspective, they suggest very positive feedback on EU pharmaceutical markets as ramipril seems to be the most suitable compound clinically.

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

3.2.1.3. Results indicating country-of-origin effects

The fact that a product has a relatively larger market share in a certain country compared to others may be due to either a preference for local manufacturers or the existence of a strong network of sales representatives. Without being exhaustive, here is a list of the most important factors:

- Ramipril (72% ACE market share in Germany, 2016) was developed by Hoescht, a German company, which then was acquired by the Sanofi group in 2004.
- Research into the French market revealed that perindopril is the leading API (market share 45.5 %), which was developed by the French Servier.
- A strong French influence can also be observed in Hungary, where the market share of perindopril products reached the highest value, 60.9%. (In Hungary, the acquisition of EGIS by Servier and the marketing activities of the Hungarian subsidiary provide an explanation for this phenomenon).
- Zofenipril: The API, developed by Menarini (IT), achieves a sales volume of above 5% only in Italy (8%) and Romania (5.4%) of all the studied countries. Both examples suggest a strong country-of-origin effect in the hypertension market.
- Research has revealed that the high market sales of enalapril in the Spanish market are probably driven by support provided by Spanish regulations.

3.2.2. Research into the diffusion of ARBs and ACE inhibitor therapies—market trends between 2001 and 2016

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

It is important to have a clear understanding of the framework of authorization and industrial property rights to provide a thorough analysis of the market entry of therapies. Since the early 1980s, ACE inhibitors were the first therapies to be authorized and launched, losing their patent exclusivity mainly in the 1990s and early 2000s. It is important to mention that in some cases manufacturers also tried to extend patent protection by infringing the law. ARBs first entered the market in 1995 and became generic from the very early 2010s.

A comparison of the population-weighted averages for the nine countries for all three years shows how the ACE-ARB market has been restructured. The average price levels of both therapeutic classes have fallen to a third or to a quarter of the original over 16 years, with price level ratios fluctuating between 2.03 and 4.00, and throughout the whole period ARB therapies

remained the more expensive ones. While in 2001 ARBs had a share of only 20.80% of DDD-adjusted sales, in 2016 they had a share of 38.22%, although growth seems to have slowed down significantly after 2009. As a consequence of this and changes in price levels, the share of revenue shifted, from roughly 70–30% of ACE-ARB to 40–60%. The ARB preference index increased from 0.19 in 2001 to 2.06 in 2009, and then changed to 1.59 in 2016. See Table 1.

Table 1 Key indicators for the ACE-ARB market (population-weighted averages for nine countries, FR, DE, HU, IT, NL, PL, RO, ES, UK) in 2001, 2009 and 2016

	2001*	2009	2016	Trend
ARB price level (EUR/DDD)	0.61	0.44	0.18	
ACEI price level (EUR/DDD)	0.30	0.11	0.07	
ARB volume (DDD, %)	20.80	34.21	38.22	
ARB revenue (EUR, %)	30.66	67.83	60.77	
ACEI volume (DDD, %)	79.20	65.79	61.78	
ACEI revenue (EUR, %)	69.34	32.17	39.23	
ARB: ACEI price level	2.03	4.00	2.57	
ARB: ACEI volume	0.26	0.51	0.61	
ARB: ACEI revenue	0.44	2.10	1.54	
ARB preference index	0.19	2.06	1.59	

* Without NL

3.2.2.2. Preference for ACE inhibitors in six European countries

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. This is illustrated in the figure below.

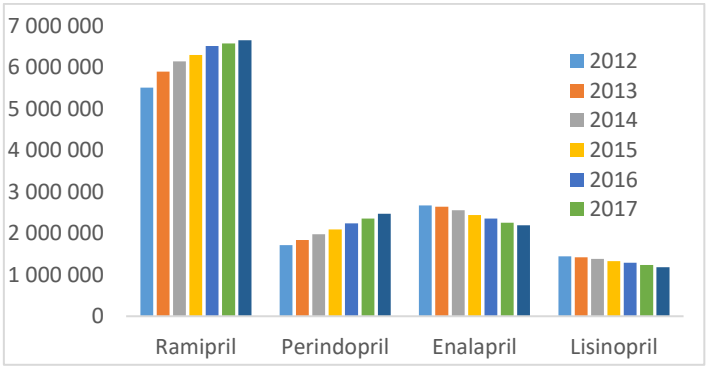

Figure 4. Annual sales volumes of the four ACE inhibitors in nine countries, 2012–2018

The figure illustrates the clear lead of ramipril in 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 has also been an increase in sales of perindopril, but sales of enalapril and lisinopril have decreased steadily. Although the distribution of the four active ingredients varies from country to country, trends are very similar for all countries over the period.

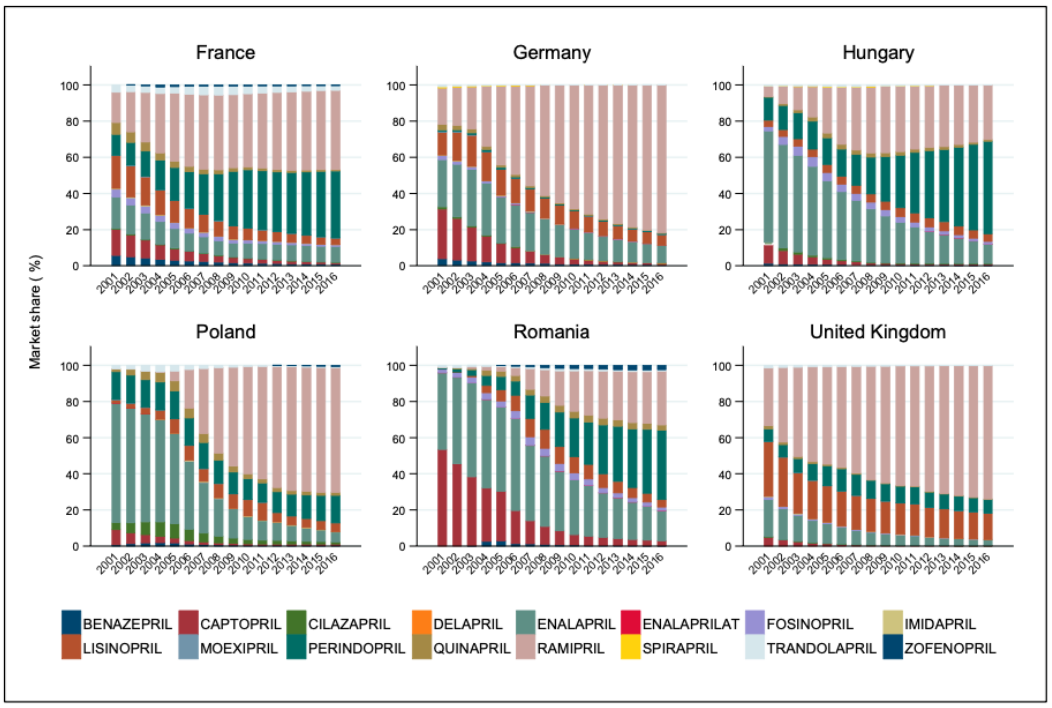

Figure 5. Volume share of ACE inhibitors (combination and single-ingredient drugs) in six European countries, 2001–2016

The market shares of DDD-adjusted volumes show (Figure 5) 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 has become the market-leading therapy. In the UK, ramipril has been responsible 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 been stable. Similarly, the market share of perindopril has been increasing in Hungary and Romania since 2008.

The focus of my doctoral research is on the process of genericization; therefore, a detailed investigation into ACE inhibitors was carried out 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 the Hungarian, Romanian, French, and Dutch markets. Enalapril remains the market leader in Spain and accounts for significant volumes in the Dutch market, and Lisinopril significant volumes in the UK and the Netherlands. Zofenopril has significantly increased its market share in the Italian market. To obtain deeper understanding of the trends that occurred after genericization, marketing research was carried out on the Hungarian market and research results were analysed in detail.

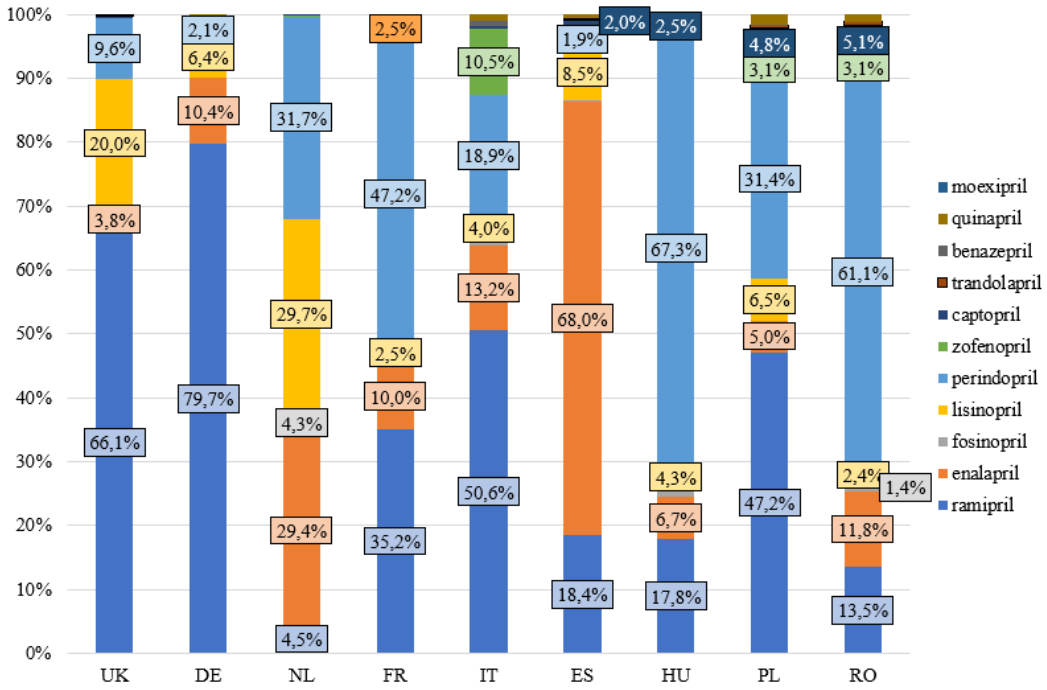

Figure 6. Market share of ACE inhibitors by volume at API level for all studied countries, 2021

3.2.3. ACE and ARB markets in Hungary in 2021

The proportion of antihypertensive drugs prescribed in 2021 continued to show the dominance of ACE inhibitors, as they were prescribed to nearly three-quarters (73.86%) of patients and physicians chose ARB inhibitors only for a quarter (26.14%) of patients. The market share of perindopril sales increased significantly to 67.3% compared to 2017, while ramipril decreased to 17.5% and captopril to 2.5%. The observed change demonstrates how significantly marketing activities can affect the market patterns of a drug class over a longer period of time. A detailed interpretation is provided in the marketing research section.

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 third and fourth place.

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

3.2.4. Marketing research

Marketing research was carried out to investigate the extent of influencing factors on prescribing decisions. At first, the responses of sales representatives and physicians to 33 statements on prescribing behaviour were compared with a view to identifying 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 when the average of physicians' responses was higher than that of the sales representatives: with Statement 3 (about clinical efficacy). In all other cases, significant differences meant a higher average score for sales representatives. Differences were revealed with the following issues: professional information (journals, pharmaceutical companies, peers, etc.), pharmaceutical companies should provide high quality offerings (samples, research support, training, brand, etc.), country-of-origin effect, and quality of drug detailing. The impact of drug-related factors (safety, efficacy, compliance, costs) on prescribing behaviour was evaluated similarly by physicians and sales representatives, in the same way that direct factors were the most significant in terms of the perception of primary product attributes (e.g., medical studies, guidelines, patient requests).

In the next step—now focusing on physicians only—factor analysis was used to group responses to the 33 statements into six dimensions. Based on the thus-generated clusters and four other statements—due to their uniqueness—the 155 physicians were classified into five clusters based on the following factors: Professional type of marketing; Marketing communication; Professional, supported pharmaceutical company; External reinforcement (patient, peers, journals, price); Regulations; Branding elements; Hungarian aspects; Medical experience/studies; Efficacy, safety of therapy. The clusters are as follows:

- Fully informed (35 persons)—physicians for whom almost everything is of above-average importance with the only exception of ‘Professional type of marketing’.
- Bureaucrats (61 persons)—for them external validation (0.264), compliance (0.320), and the efficacy of the therapy (4.950) were the most important aspects. ‘Professional type marketing’, on the other hand, is considered the least important factor (-0.357).
- Sensitive to brands and country of origin (33 persons)—for them, the most important thing is that drug production is based in Hungary (0.291), and they also find ‘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

they are least concerned about their 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)—these individuals 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); similarly, the safety of the drug therapy and side-effect profile is of least importance to them (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 study (5.000) are essential, professional type of marketing is of high importance (1.914), they seem to need no external validation (-2.188), branding elements are also seen as unimportant (-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 for them as well.

First, the prescription frequency of different APIs was examined to identify whether this was different across the five clusters. Significant differences were found in several cases, as follows:

- Ramipril is generally included in one of six prescriptions as an API, except for those 'Sensitive to drug detailing', who choose it only once 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 three or four times in every ten.
- 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 these drugs 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.

The questionnaire included a question asking the following: 'Out of all the ACE inhibitors and ARB inhibitors, which one do you prescribe more often to your patients?'. There was 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 of 'Fully informed', 'Bureaucrats', and 'Sensitive to brands and country of origin', 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 prefer ACE inhibitors (100%), while the 'Efficiency seekers' group is the least likely to select ACE inhibitors (31.6%), but prefer 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 7).

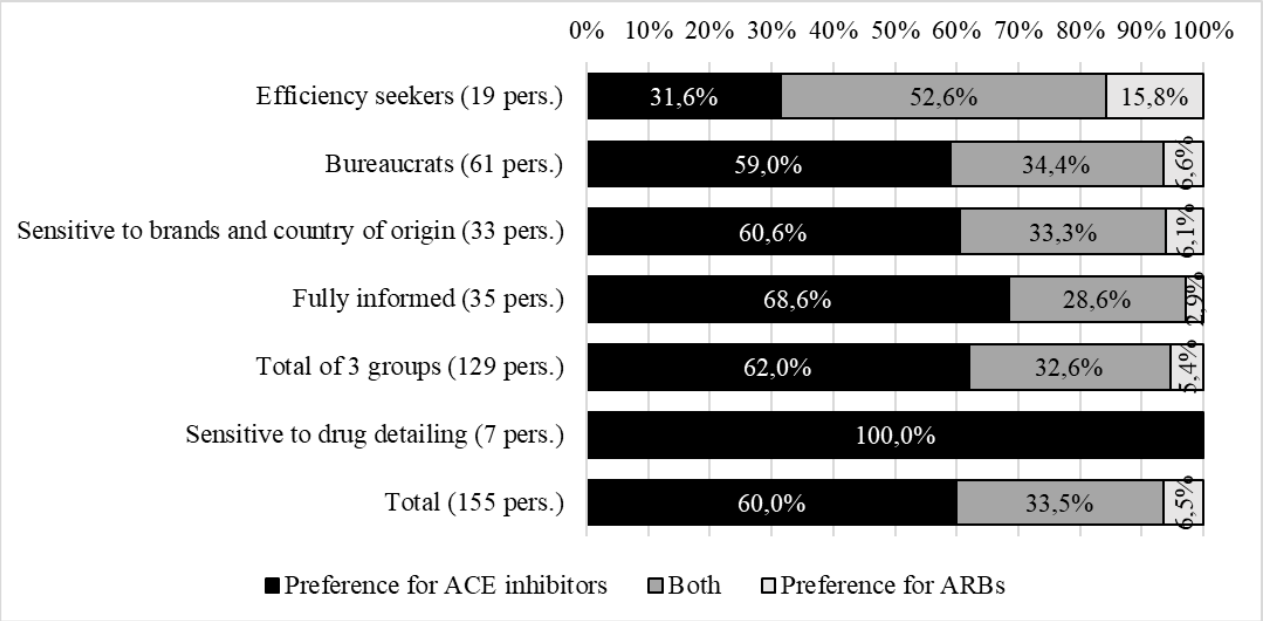

Figure 7. Distribution of physicians with a preference for ACE inhibitors and those with preference for ARB inhibitors by cluster

4. Summary of conclusions

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 on and can subsequently determine market performance. In the qualitative research I defined a framework that combines evidence-based medicine with a marketing approach to address the main research question. Results revealed that clinical appropriateness plays a role almost without exception for all factors that have an impact at the level of APIs, but it is by no means the sole nor dominant factor in relation to the complex interrelationship among the purchasing decisions associated with the pharmaceutical industry.

On the one hand, the comparison of ARB and ACEI therapies highlighted 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 considering the ranking of evidence-based principles. Figures also confirm that only innovative products with the similar or the same efficacy and safety profile can compete in the pharmaceutical market. Therefore, from a marketing point of view, competition within need and product groups favours solutions with more appropriate product attributes. The difference between Eastern and Western Europe was also demonstrated by Denig and Rogers' models: in Eastern Europe, the penetration of clinically more beneficial molecules is enhanced by genericisation (late entrants), while in Western Europe higher prices are less of a barrier to diffusion in the innovation phase, so that penetration occurs earlier. 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 a 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, lowering 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. The analysis of secondary data revealed that the impact of marketing activities can only be interpreted to a limited extent on API-level aggregated data, therefore investigating data at the brand level is suggested. The results suggest a country-of-origin effect in several cases.

In conclusion, genericisation 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, API genericisation 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. 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' perception is key to understanding the trends that ultimately lead to the prescription of different APIs and their market performance accordingly. To measure the impact of these factors, I conducted a quantitative survey among physicians and sales representatives using a non-representative sample and online interviews.

Physicians generally consider drug-related and direct types of information to be the most important decision-influencing factors; these convey professional data and facts originating

either from their own studies or from prescribing guidelines or from sales representatives. The opinions of physicians and sales representatives seem to differ significantly in relation to several factors, mainly related to marketing activities, where the phenomenon of expected responses may have distorted the outcome.

I believe that the major achievement of my doctoral research is the construction of a theoretical framework that describes the interplay between clinical evidence and marketing performance in detail. The last figure reveals how the diffusion of pharmaceutical therapies takes place and includes suggestions about how to investigate the market patterns that emerge as a result of competition (cross-sectional and longitudinal analysis of secondary data at API and brand level using a sample that spans 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 prescribing factors of most influence 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 into the evaluation. Since the market performance of drug therapies is explained as a result of physicians' prescribing decisions, secondary market data and findings from the primary marketing research are compared and contrasted, and the factors influencing prescribing decisions are examined through cause-and-effect relationships using market performance data.

I believe that general conclusions at the level of active ingredients should only be made with an understanding of the complexity of the pharmaceutical industry, and by combining various disciplines. In addition to the theoretical and practical recommendations, and in relation to the therapeutic regimens for hypertension, an analysis of two API classes with different mechanisms of action was also carried out. I believe that the related framework that was constructed is applicable for the analysis of any similar therapeutic drug class (e.g., antipsychotics, diabetes drugs, contraceptives, etc.).

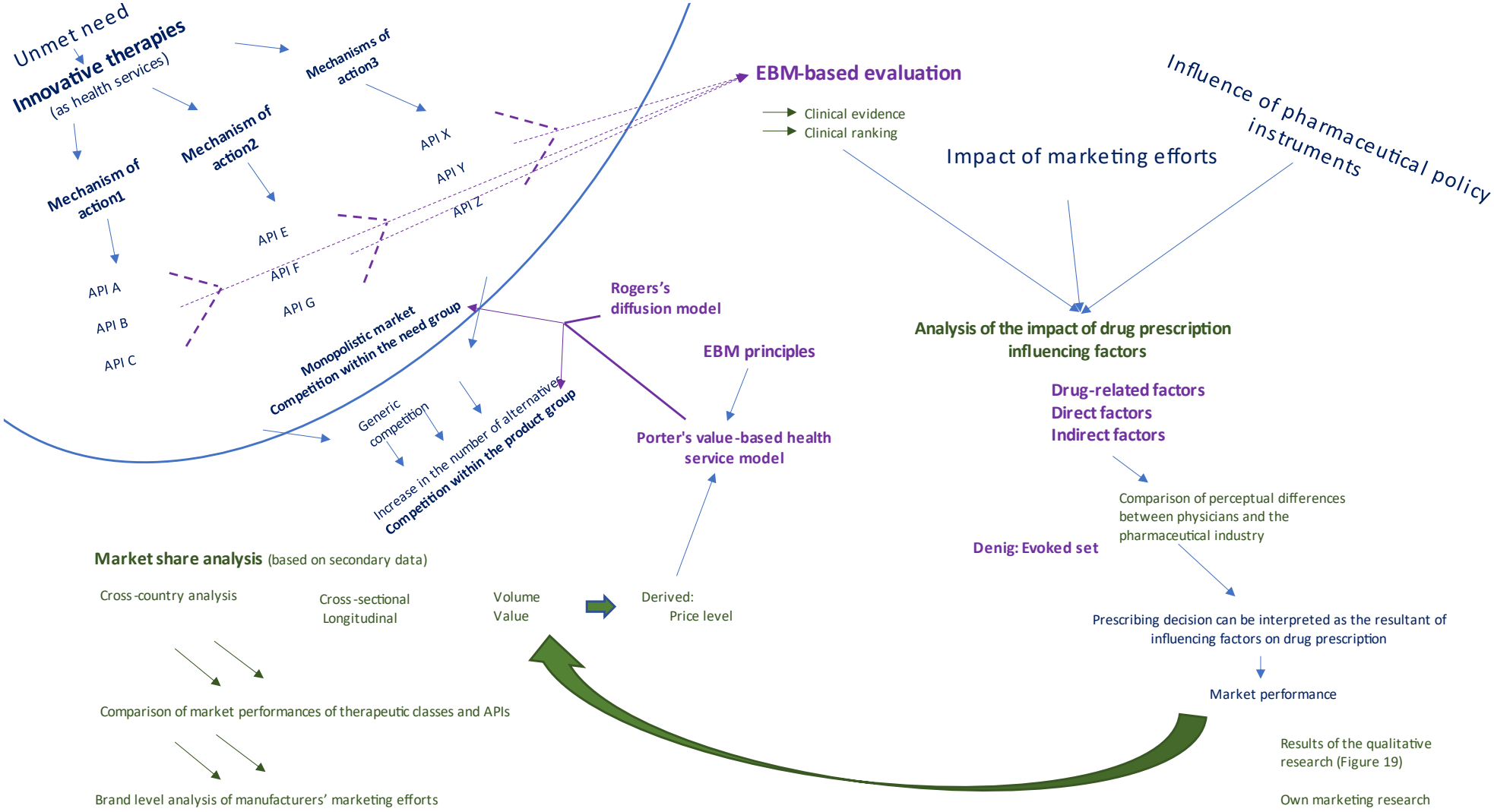

Figure 8. Schematic diagram of the conceptual and analytical framework resulting from the doctoral research

5. Author's own publications about the related topic

Bence Kovács; Miklós Darida; Judit Simon
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Vezetéstudomány 48 (Budapest Management Review): 5 pp. 49-63, 15 p. (2017)

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International Journal Of Clinical Pharmacy 44: 1 pp. 290-291. , 2 p. (2022)
Abstract

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In: Keresztes, Gábor; Kohus, Zsolt; Szabó P., Katalin; Tokody, Dániel (szerk.)
Tavaszi Szél 2017 Konferencia. Nemzetközi Multidiszciplináris Konferencia : Absztraktkötet
Budapest, Magyarország : Doktoranduszok Országos Szövetsége (DOSZ) (2017) 477 p. p. 252
Közlemény:3224817 Nyilvános Forrás Könyvrészlet (Absztrakt / Kivonat) Tudományos

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Gyógyszerterápiák piaci teljesítményének elemzése az európai gyógyszerpiacokon (Market Performance Analysis of Pharmaceutical Therapies in European Pharmaceutical Markets)
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Gyógyszer-hatóanyag terápiák értéke és azok piaci teljesítményének összehasonlítása Európában (2016) (Comparison of the value and market performance of active ingredient therapies in Europe)
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