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SPECIFICITY OF THE INTERNATIONAL ACTIVITY OF THE PHARMACEUTICAL COMPANIES IN BULGARIA

ABSTRACT

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The dissertation consists of an introduction, three chapters and a conclusion, a list of references and appendices. It comprises 222 pages, of which 200 pages are the main text-statement and 22 pages the list of sources and appendices used. The exposition contains 47 figures and 24 tables. The appendices contain: Questions from an in-depth interview with specialists in the field of international trade and import of medicines in Bulgaria; Inquiry to the Customs Agency to provide data concerning the import/export to/from the territory of the Republic of Bulgaria from/to third countries of medicines under CN headings (3004 10; 3004 20; 3004 31; 3004 32; 3002; 3004 41; 3004 42) placed under customs regimes and admitted for free circulation and release for consumption (procedure code 40 and procedure code 10). The sources used include 29 monographs and studies, 50 articles, 79 electronic sources. The author of the thesis is a full-time PhD student in the Department of International Economic Relations.

I. General Characteristics of the Dissertation

Today's dynamic environment, underpinned by increasing globalization processes, intensive technological development, and economic and demographic fluctuations, poses a number of challenges to the regulated pharmaceutical industry. In the context of global economic integration, the well-being of nations, and access to goods, to medicines, etc., depends to a significant extent on the development of international trade. The pharmaceutical industry is a sector of existential importance that ensures the production and supply of medicines. Health and economic prosperity are fundamental to maintaining the well-being of nations. The social dimensions are related to securing medicines, minimizing drug shortages, and managing equitable access to needed medicines. There is a need to meet the needs of patients, minimize shortages and, in parallel, provide medicines without compromising quality. The political and legal dimensions of relevance relate to regulations in the sector, the balance between strict adherence to sustainable procedures, and the need for timely and flexible decisions and actions in the event of a change in the environment. Predictability in the sector would help health systems cope with a range of challenges, including pandemics, and health and economic crises. It is in times of crises that the issue of trade and the supply of medicines to markets is of overwhelming relevance. The study of this market, the identification of trends, possible responses, specific solutions, actions taken and results achieved are of scientific and practical interest.

Since Bulgaria acceded to the EU in 2007, the legislation in the pharmaceutical sector has been harmonized to a significant extent with the EU regulatory framework. Therefore, tracking the dynamics of trade and production of medicines before and after 2007 would show what the effects of membership have been on the pharmaceutical industry in the country. The topicality of the dissertation is dictated by the need for a comprehensive study of the sector and the pharmaceutical companies-Bulgarian and foreign-that produce and import medicines in the country. The focus is on the established commercial practices as well as on the current perspectives that should solve several problems of economic, social and political nature.

A review of the scientific literature shows that there is relatively little interest and the theoretical formulation of international trade in medicines. This conclusion applies mostly to the Bulgarian specialized literature. However, the importance of fair, flexible, and sustainable supply chains for medicines is growing and should be instrumental in achieving ethical trade within the EEA. Trade policy for health products is critical, highlighting the importance of international cooperation, especially in an unpredictable economic and social environment. The choice of the topic of this dissertation - "Specificity of the international activity of the pharmaceutical companies in Bulgaria", is dictated by several reasons.

First, the study of the international activities of the pharmaceutical industry poses a complex task for practitioners and scholars and provides an opportunity to interpret and explore various issues. The aim is to identify trends that can explain and predict the development of the sector, even in an environment of economic and social crises. Understanding this activity in the context of national and supranational policies will enable organisations working in this sector to make informed decisions and develop effective strategies and practices in order to supply markets with medicines in an equitable and sustainable manner.

Second, the author's individual motives for choosing the topic of this dissertation are related to his scientific interests in the field of trade in medicines, and more specifically in the marketing of medical products on the Bulgarian market. The Covid-19 pandemic has challenged a number

of EU countries and the effects of the crisis in the pharmaceutical industry have been observed for years afterwards. It is essential to identify the causes of shortages of certain medicines, as well as to highlight good practices and national measures to prevent such adverse reactions due to unpredictable circumstances such as health and economic crises.

The object of the study is pharmaceutical companies operating on the domestic market. These are foreign companies that import medicinal products on the domestic market, Bulgarian companies-manufacturers and licensed importers of medicines whose activities are regulated by the state, the IAL, professional organizations, patients and hospitals.

The subject of the study is the commercial activity in the pharmaceutical sector and the changes that occur with significant changes in the external environment.

In relation to the subject and object of the study, the main aim of the dissertation is to find out the specifics and trends of the Bulgarian market in the import, production, and trade of medicines. To achieve the main objective, the following research tasks were set:

1. Theoretical and methodological: to systematize and analyze the scientific literature on international trade, the different approaches, and the specifics of the activity.

2. To study the organization of the pharmaceutical business and trade in medicines in Bulgaria.

3. To highlight both good and controversial practices in international trade in medicines.

4. To conduct a study on the trends of import of medicines in Bulgaria.

5. Based on the theoretical and methodological research and empirical study we make generalizations, conclusions, and assumptions for the development of the sector.

The main thesis of the dissertation is that parallel importation and importation of generics can ensure the continuity of the supply of medicines to guarantee access to medicines by patients in the country.

Hypothesis 1: Imports of medical products in Bulgaria have grown significantly since Bulgaria joined the EU.

Hypothesis 2: The Covid-19 pandemic has an impact on the realization of drug supply in the country.

Hypothesis 3: Parallel trade contributes to getting missing medicines to the market through imports.

Hypothesis 4: The import of generic medicines in the country is witnessing significant growth for the study period 2018-2022.

The research methodology in this dissertation is based on traditional research approaches and methods such as: systematic approach and theoretical analysis of literature (chapters one and two); conducting in-depth interviews and qualitative analysis of the information learned from the interviews (chapter two) and cluster analysis (chapter three). All chapters of the dissertation

also employ other qualitative methods to investigate the phenomena - comparative method, analogy, synthesis, deduction, and induction.

This dissertation also has several limitations of a heterogeneous nature that create its framework:

- The study is limited to tracking the dynamics of parenteral imports, as well as those of generics, antibiotics and vaccines.
- The period over which trends in imports of medical products into Bulgaria is monitored to track the dynamics of activity before and after the country's entry into the EU is limited to 2003 to 2022.
- The study of the activities of pharmaceutical companies that market their medicines on the Bulgarian market is limited to a 5-year period - from 2018 to 2022.
- The dissertation will not present some of the data that we have in terms of value and quantity, as well as the trade names of the drugs that pharmaceutical companies sell on the Bulgarian market, due to the nature of this business and the confidential information that does not allow it to be subject to public access.

The information needed to achieve the aim and objectives of the thesis is provided by:

- theoretical study of numerous publications of foreign and Bulgarian authors;
- international and empirical research results;
- secondary data from Bulgarian and foreign institutions;
- statistical data from private companies to analyze and interpret results and trends.

Chapter one of the dissertation is theoretical and conceptual, its main aim being to lay the theoretical foundations for an in-depth theoretical and practical study. The chapter examines the significance of globalization, regional integration, and economic welfare, and how these affect international trade in medicines. The chapter also identifies the international organizations, regulatory bodies, and alliances that regulate trade in medicines. Emphasis is also placed on pharmaceutical TNCs as a major part of new trends in international business and global competitiveness in international markets. The chapter concludes with an analysis of the impact of COVID-19 on supply systems in the pharmaceutical industry.

Based on the theoretical views presented in the previous chapter, *chapter two* presents the organization of the pharmaceutical business and trade in medicines in Bulgaria. The legislative framework in Bulgaria for the wholesale of medicines is covered, and the main practices related to medicines policy and the basic terminology are outlined. The way supply chains are built and function in the wholesale of medicines is illustrated. To draw a parallel between chapters two and three and to set the foundations on which the cluster analysis will be carried out, the second part presents the meaning and scope of parallel trade in medicines. Emphasis is also placed on the controversial practices on the Bulgarian market as well as some of the possible reasons for the shortage of certain medicines in the country. Based on the theoretical views presented in the previous chapter, chapter two presents the organisation of the pharmaceutical business and trade in medicines in Bulgaria. The legislative framework in Bulgaria for the wholesale of medicines is covered, the main practices related to medicines policy and the basic terminology are outlined. The way supply chains are built and function in the wholesale of medicines is illustrated. In order to draw a parallel between chapters two and three and to set the foundations on which the cluster analysis will be carried out, the second part presents the meaning and scope of parallel trade in medicines. Emphasis is also placed on the controversial practices on the

Bulgarian market as well as some of the possible reasons for the shortage of certain medicines in the country.

Chapter three presents the empirical study. The scope, objectives and data sources of the empirical study are presented. Then, the chapter continues with the analysis of the data extracted according to the information sources. The conclusion of the dissertation verifies the main thesis and hypotheses.

The work contains tables and figures that illustrate the important aspects of the study, as well as a list of references used.

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III. Summary of the dissertation

Chapter One: Impact of globalization, TNCs, and international organizations on trade in medicines

In chapter one, the author builds the conceptual framework of international trade and interconnections in the pharmaceutical sector as a basis for the development of TNCs and international organizations. At the beginning of the chapter, the main concepts such as "globalization" and "regional integration" are discussed. A review of researchers' understanding of globalization is made - what are the definitions of different authors and which are perceived as the most appropriate for this thesis. Based on the interpretations of the term and following the research objectives of the study, an author's definition is proposed, namely:

Globalization is a set of interconnected processes involving people, companies and countries to intensify transnational linkages as well as bridge distances and existing divides between them.

For the purpose of this study, it was necessary to present globalization processes as a prerequisite for companies to internationalize their activities, creating the opportunity to distribute their products and services internationally. The work points out the different manifestations of globalization that societies are facing:

- *In the economic sphere,* globalisation is expressed in the free movement of capital and goods, which accompanies the liberalisation of financial markets and eases or completely removes restrictions on international trade, which creates both conditions for stimulating some national economies and negative consequences for others. Intensified competition forces companies to seek new sources of competitiveness.
- *In the public sphere,* globalisation is changing the way nations communicate. Traditional channels of communication have been replaced by social networks and

communication platforms. Societies have access to cheap and easy methods of communication thanks to a dynamic technological environment. The media facilitate the rapid dissemination of information and political and social claims in a unified information space. Phenomena such as outsourcing, working from home, online shopping, etc. are on the rise.

- *In the field of education,* globalization facilitates the circulation of students and staff, access to information allows the exchange of experiences between different countries, shortens the distance and cultural differences between nations, helps to broaden the world view, increase the quality of educational services. Global education is an educational perspective based on the fact that modern people live and interact in an increasingly global world. The emphasis is on education providing learners with opportunities and competencies to reflect and share their perspective and role in a global, interconnected society. Prompting dialogue on common social, environmental, political, and economic issues is at the heart of implementing new ways of thinking and subsequent action.
- *In the field of ecology,* the impact of globalization processes remains controversial. As prof. Margarita Boneva stresses in her report "Globalization and Ecological Crisis", the ecological problem of the contemporary world is not only acute, but also multifaceted. It manifests itself in practically all branches of material production, especially in agriculture, the chemical industry, ferrous and non-ferrous metallurgy, and nuclear power, and is relevant to all regions of the planet.
- *In pharmaceuticals*, intensive M&A activity has emerged from increasing globalization, in particular during the period 1995-2005, starting with the mergers between Astra and Zeneca, Ciba-Geigy and Sandoz, Pfizer and Warner-Lambert, Sanofi Aventis, and GlaxoSmithKline, culminating in the Pfizer-Pharmacia merger in 2003. The push towards the 'bigger is better' model has resulted in large-scale operations around the world - large R&D centers, armies of sales offices, multiple manufacturing sites, and often confusing and matrixed management layers - all further complicated by the lack of cultural integration of the combined firm. Industry consolidation is justified by economies of scale, diversified portfolios, and businesses across the healthcare spectrum. The industry continues to face the challenge of integrating dispersed research units and therapeutic areas across the combined companies. Localizing their research units in these hotspots allows big pharma scientists to work closely with outside researchers and clinicians in progressing their drug pipeline, through a much more open and collaborative model.

For a more objective analysis, chapter one of the paper presents both the positive and negative effects of trade liberalization. The benefits of globalization include:

- the existence of a global market where companies and customers benefit from better access to products and services;
- there has been an increase in the manufacturing sector as there are opportunities for investment in countries with lower barriers to entry and lower paid labour without compromising on the skills of employees;
- there are opportunities for people to interact and communicate across borders;
- information exchange is growing, and thus cultural differences are being mitigated, information flows are increasing, diffusion of new technologies and know-how is taking place, and these are making a significant contribution to societies;
- the world becomes more accessible, with many alternatives and different opportunities for education, work and development;
- migration from high-risk regions to safe ones is possible;
- because of the interconnectedness of societies, the economy of one country depends on another, leading governments to try to increase the economic balance between them;

- international trade leads to economic growth when national exports grow and countries that import benefit from lower-priced goods and services;
- countries can rely on foreign aid in crises;
- the sense of isolation in developing countries is reduced, etc.

As a consequence of globalization, the following disadvantages are also observed:

- many people in developed countries lose their jobs as companies pursue the option of "outsourcing" to developing countries where the cost of labor is low and company profits are substantial;
- the increasing pace of trade with China and other low-wage countries is accelerating the decline in manufacturing employment in the developed world, putting societies in difficulty;
- when exporting production processes, the parent country loses the revenues accumulated in the developing country;
- globalization can lead to a loss of cultural identity as transnationals pick up Western ideas;
- globalization leads to extremely unequal outcomes and does not solve the problem of the social gap between rich and poor, on the contrary, the rich accumulate ever greater profits while countries in Africa suffer from a lack of investment;
- due to the interconnectedness of economies, sustainability is not guaranteed - a shock in one developed economy has a tangible impact on other countries;
- the environment is destroyed because of heavy industries in countries with lower environmental barriers;
- industrial development facilitates the maintenance of nuclear weapons, nuclear, chemical, and biotechnological accidents are possible;
- unsustainable energy consumption, unilateral treatment of global resources, transport pollution ;
- high likelihood of global recessions due to interconnected economies.

The COVID-19 pandemic poses challenges that lead to shortages and price increases and could potentially fuel an epidemic of counterfeit and substandard medicines, including:

- severe disruptions to supply chains caused by significant reductions in air freight capacity, sea freight, and transport logistics;
- national export restriction measures are being introduced by supplier countries relating to both Covid-specific goods but also non-Covid (e.g. India bans several key active pharmaceutical ingredients (APIs) and finished products, although some of these bans have been lifted; UK bans parallel exports; EU restricts exports of protective equipment.)
- there has been a slowdown in drug production in the affected countries in China, as well as in key manufacturing bases in India.

The economic and social crises that have occurred globally demonstrate, on the one hand, the interconnectedness of states and, on the other, their inability to cope collectively in such turbulent times. In the first place, the virus is causing a humanitarian crisis facing the health systems of dozens of countries. The growing importance of the pharmaceutical business and trade in medicines is proportionate to the ever-increasing human need for adequate and timely treatment through innovative pharmaceutical products. The accessibility of advanced medicinal products globally is largely dependent on the rapid manufacturing, economic and strategic processes that pharmaceutical companies implement.

Parallel to globalization, an alternative process is developing - namely regionalization. The geopolitical, geo-economic and social world economy is being redistributed through regionalization. In world experience, five main types of economic regionalization can be distinguished: Free Trade Area; Trade Union; Common (Single) Market; Economic Union; Monetary Union. These are described in detail in the paper to highlight the stages of integration and the impact of integration processes in the contemporary economic environment.

On the other hand, welfare in economic terms, is central to national policy making. The development highlights the interlinkages between public welfare, health, and economic life. The public welfare function has three main characteristics:

- the well-being of society depends only on the well-being of its members;
- societal well-being is a function of the well-being of each member of society;
- the proportion in which society is willing to reduce the welfare of one individual by one unit while increasing the welfare of the other individual by a certain amount of units depends on the degree of inequality.

The paper focuses on one of the essential indicators that reveal the level of social welfare in a country, namely the health status of its citizens. Individuals' good health is simultaneously an asset and a source of economic and social stability through which strong, dynamic, and creative societies are achieved. In personal terms, well-being and quality of life is a conditions for health, but good health is also a condition for well-being and quality of life.

The basic objectively measurable condition of human existence is health. Without it, the well-being of nations cannot be achieved therefore health protection is the main task of socio-economic life. International cooperation in the field of medicinal products is based on this interrelationship. Since the theme of the work is related to the activities of pharmaceutical companies and the supply of medical products to markets, the paper presents the international organizations that, through their functions, policies, and mechanisms ensure the equitable and sustainable access of countries to medicines. These are the World Trade Organization (WTO); the World Health Organization (WHO), the EU, and its pharmaceutical regulatory systems and directorates. Their activities and functions are described in detail in the thesis. Of particular relevance to the aims of the thesis is the focus on the EU legal framework for medicinal products for human use. It sets standards to ensure a high level of protection of public health and the quality, safety, and efficacy of authorized medicines. It stimulates the functioning of the internal market with measures to promote innovation. A key requirement for a medicinal product is authorization by the competent authorities before it can be placed on the market. Negative experience shows that to protect public health, a medicinal product should not be placed on the market without prior authorization.

A large body of legislation has been developed around this principle, with the gradual harmonization of marketing authorization and post-market monitoring requirements applied across the European Economic Area (EEA). The European Medicines Agency (EMA) and Member States cooperate and exchange expertise in the evaluation of new medicines and new safety information. They also rely on each other to exchange information related to the regulation of medicines, for example on adverse reactions to medicines, supervision of clinical trials, conducting inspections on medicine manufacturers, adherence to Good Clinical Practice (GCP), Good Distribution Practice (GDP) and Good Pharmacovigilance Practice (GVP). The system in Europe offers different ways of obtaining authorisation for medicines. The centralised procedure allows a medicine to be brought to the market on the basis of one EU-wide

assessment and one EU-wide marketing authorisation. Pharmaceutical companies send one application for authorisation to the European Medicines Agency (EMA). The EMA's Committee for Medicinal Products for Human Use (CHMP) carries out a scientific assessment of the application and issues a recommendation to the European Commission on whether the medicinal product should be authorised. Once the European Commission has granted authorisation under the centralised procedure, it is valid for all EU Member States. Obtaining authorisation through the centralised procedure is mandatory for most innovative medicines, including those for rare diseases. Most medicines authorised for use in the EU are not covered by the centralised procedure. They are assessed by the national competent authorities (NCAs) in the Member States. When a company wants to obtain authorisation for use in only a few Member States, it can use one of the following procedures:

- a decentralised procedure where companies can apply for simultaneous authorisation of a medicine in more than one EU Member State if it is not already authorised in any EU country and does not fall under the centralised procedure;
- a mutual recognition procedure where companies whose medicine is authorised in one EU Member State can apply for recognition of that authorisation in other EU countries. This process allows Member States to refer to each other's scientific assessments. The rules and requirements for pharmaceuticals in the EU are the same regardless of how a medicine is authorised for use. An important feature of the EU medicines regulatory system is the transparency of its work and the way it makes decisions.

The first chapter deals with the importance of the EU's Common Commercial Policy for trade in medicines. The GTP has a strong supranational character- member states almost lose their sovereignty in the area. The paper presents the chronological development of the GSP through a network of trade agreements over the last 60+ years. At the heart of this policy is the expansion and consolidation of the single market through a series of treaties to ensure the EU's competitiveness in a globalised world. The most important instruments of this policy are: the common customs tariff; the common import regime; specific import safeguard measures; and the common export regime. Their functions are described in detail in the dissertation in order to draw a parallel to the data that show the dynamics of trade development in the EU, and more specifically that of medical products. As Europe is the second largest pharmaceutical market in the world and accounts for 22.2% of global pharmaceutical sales, the chapter graphically illustrates the evolution of EU trade in medical products from 2002 to 2020, along with the share of medical products in total EU trade 2002-2020; and the evolution of trade in medical products between the EU and the United States from 2002 to 2020, among others. The first chapter also shows a forecast of the growth of European pharmaceutical markets compared to global markets between 2019 and 2024. The European Union member countries are projected to experience a 3.9% growth in the pharmaceutical market over the given period.

The fourth section of the chapter deals with the dynamics of mergers and acquisitions and innovative development in transnational corporations (TNCs) in the pharmaceutical industry. It focuses on the phenomenon discovered by researchers Sherer and Comanor that pharmaceutical innovation productivity has been declining in recent years and one of the main reasons for this is the wave of mergers and acquisitions by big pharmaceutical leaders. It is becoming clear that the group of large companies that are the leading drivers of pharmaceutical research and development is becoming increasingly concentrated. The development identifies the leading pharmaceutical companies by their post-2020 revenues and their most significant mergers and acquisitions. As R&D is critical to the growth and future success of research-based pharmaceutical companies, to increase their efficiency, pharmaceutical companies are

beginning to reduce R&D spending and try to gain access to external knowledge specifically through mergers and acquisitions. The low success rate of pharmaceutical research and development, combined with long development times, leads to extremely high costs for the discovery and development of a new drug.

The chapter concludes by examining the impact of COVID-19 on drug delivery systems. The COVID-19 pandemic demonstrates both the opportunities that can minimize economic and social damage in times of crisis and the negative effects caused precisely by the increasing connectivity of markets. Table 1 presents the opportunities for the pharmaceutical sector as well as the negative effects caused by COVID-19 in an internationalization context.

Table 1. Opportunities and negative effects arising from COVID-19

Opportunities	Negative effects
Implementation of rules and practices that have already been adopted, applied, and established in foreign markets	Faster spread of disease due to open markets
Interaction of countries in policy implementation following the pandemic crisis	Impact of Foreign Policy on Medical Ingredient Dependent Markets
Reorganization of medical supplies; the possibility of sourcing from different markets to minimize production costs	Shortages of certain medical products due to dependence on production and supply from foreign markets
Need to stimulate the production of medicines and pharmaceuticals in local markets	Production shortages in local markets
Accelerated/relaxed authorization procedures for "old" products	Risks of increased circulation of counterfeit medicines

Table 1 was made by the author.

Generalizations made as a result of the theoretical review in the first chapter create a prerequisite for the study of the organization of the pharmaceutical business in Bulgaria, as well as the regulatory framework that regulates the sector in the country.

Chapter Two: Organization of the pharmaceutical business and trade in medicines in Bulgaria

As a member of the EU, Bulgaria is also bound by the European medicines regulatory system. The rules governing the manufacture and marketing of medicinal products in the European Union are largely harmonised, covering almost the entire life cycle of a medicinal product, starting from the conduct of clinical trials (Directive 2001/20, 2005/28), through manufacturing (Directive 2003/94), registration, distribution and pharmacovigilance (Directive 2001/83) to the principles on pricing and reimbursement (Directive 89/105).

The chapter presents the legislative and regulatory bodies in relation to the pharmaceutical sector in Bulgaria and their functions. These are the Parliament; the Government; the Ministry of Health; the EMA (European Medicines Agency); the EC (European Commission); the EMA (Executive Medicines Agency); the NHIF (National Health Insurance Fund); the Ministry of Economy and the Consumers Association. The main laws and regulations governing the sector in Bulgaria are also presented. The regulations for the wholesale of medicines on the territory of the Republic of Bulgaria under the Medicinal Products in Human Medicine Act (MPHMA)

are also discussed. The main document developed by WHO that regulates the requirements for the distribution of medicinal products is Good Distribution Practice (GDP) with the main task of ensuring that manufactured and marketed medicinal products are distributed to patients with the necessary quality. This level of quality must be maintained through the distribution network so that medicines are allowed to circulate in the population without altering their properties.

The implementation of the principles and requirements of GMP in the country became possible through changes in the Bulgarian Medicines Act in 2000. Compliance with these practices is of utmost importance, as in recent years in the EU and worldwide, there has been an alarming increase in the market penetration of so-called "counterfeit" medicines (fake medicines). These products usually contain sub-groups (lower quality) or fake ingredients, or contain incorrectly dosed ingredients or active substances. The control and regulation of supply help to limit attempts to distribute counterfeit medicinal products. Stakeholders in deterring access to counterfeit medicines on the market are many - manufacturers, pantent carriers, licensed suppliers, governments, patient and doctor organisations. Experience has shown that counterfeit medicines not only enter the market through illegal means, but are distributed through legal channels and distribution chains (distribution) of drug manufacturers (importers), wholesalers and retailers (pharmacies and drugstores).

The main activity of the IAL is the authorization of the use of medicinal products on the territory of the Republic of Bulgaria. Licensed wholesale distributors of medicinal products must have appropriate premises, equipment, and facilities, and suitable means of transport to ensure the proper storage, distribution, and transport of medicinal products by the requirements of Good Distribution Practice.

The procedure for the issuance of wholesale authorization for medicinal policies is graphically presented in the development. In the procedure for the granting of wholesale authorisations for medicinal products, the IAL assesses the documentation and carries out an on-site inspection of the premises specified in the application to establish their compliance with the requirements of Good Distribution Practice. Data on applications for authorisations for use submitted by 2020 are provided.

At the heart of medicines policies are access to medicines and the management of medicines costs. The affordability of medicines is viewed from two aspects-physical and financial. In terms of ensuring the physical availability of medicines, it is necessary to have a system of wholesale medicine warehouses and pharmacies and to have a system for authorizing the use of medicines and their importation or manufacture. Health spending in Europe has been increasing progressively in recent years, which has made reforms of health systems one of the priority objectives for European and national policies. The impetus to reduce public and private spending necessitates the consumption of 'generic medicines'. The WHO glossary definition has been adopted, according to which a generic product is that pharmacological product, usually intended to be interchangeable with the product of the original brand, manufactured without a licence from the manufacturer of the original product, and marketed after the patent or other exclusivity rights of the original medicine have expired. Generic medicines shall be marketed either under a nonproprietary name or under another approved name and not under a proprietary or trade name. The generic medicines policy is understood as a system of measures that support the production and distribution of medicines with expired patent protection. The study attempts to establish whether the import of generic medicines into the country has been increasing in recent years and whether this is a sustained and long-term trend.

Chapter two also presents the supply chains in the wholesale of medicines. The following activities are illustrated graphically: the life cycle management framework for medicines; supply chain channels for medicines; distribution channels for medicines and other figures that show the sequence of the marketing and supply processes for medicines. The types of wholesalers are indicated, which differ according to whether they own or only temporarily handle the medicines. According to this specificity, they are:

- wholesalers - have ownership of the goods and assume all risks and responsibilities for their storage;
- commercial intermediaries - negotiate transactions in medicinal products between manufacturers or importers and wholesalers;
- sales branches - similar to the first tier of wholesalers, but distributing products of a single manufacturer, whom they represent within the country or for a specific region;
- representative offices (sales offices) - liaise between the manufacturer and its distributors in the territory for which they are responsible, without carrying out commercial activities.

The significance and scope of parallel trade in medicines is further discussed. Parallel trade is a legal activity in the EU and for the territory of the Republic of Bulgaria, and is regulated in Chapter Nine (title amended, SG No. 71 of 2008, in force 12.08.2008) of the National Law on Medicinal Products in Human Medicine (LPPHM). In general, parallel trade in medicines is divided into import and export. The import aspect of this trade has been extensively studied from a legislative point of view. A parallel imported medicinal product may only be distributed on the Bulgarian market if the importer holds a valid parallel import authorization for the product issued by the IAL. In the Bulgarian HCMP Act the definition of parallel import medicinal products is set out in Article 214 (1); (2) and reads as follows: "a medicinal product authorized for use in another Member State may be imported in parallel into the territory of the Republic of Bulgaria when it is identical or similar to a medicinal product authorized for use in the Republic of Bulgaria.

A controversial practice arising from the possibility of parallel export of medicines is the price pressure from the so-called "reference countries". According to the National Council on Drug Pricing and Reimbursement and the Medicines Act, the state regulates the ceiling prices of prescription drugs. The law regulates the prices of medicinal products included in the Positive Medicines List (PML) and paid for with public funds in accordance with the lowest reference prices in EU member states. The Ordinance on the conditions, rules, and procedure for the regulation and registration of the prices of medicinal products (amended and supplemented, State Gazette No. 26 of 29 March 2019) identifies 10 countries to which Bulgaria refers: Belgium, Greece, Spain, Italy, Latvia, Lithuania, Romania, Slovakia, Slovenia and France. Countries focused on expanding healthcare coverage are increasingly using external reference prices for pharmaceuticals. The scant evidence suggests that reference pricing appears to lead to narrower pricing windows, with the risk of price decreases in high-price countries and price increases in low-price countries. External reference pricing, also known as international reference pricing, international price comparisons, or cross-reference pricing, is set by WHO and is a policy in which a government compares the price of a medicine with one or more other countries to derive a reference price for setting or negotiating the price or rate of return of a product in that country. External reference prices are a price regulation tool used to contain costs and to ensure that the price paid for a pharmaceutical product in a particular country does not unduly exceed the price paid for the same product in the reference country . Reference

pricing policies are often seen as progress in building and expanding health systems to universal health coverage. In this way, a low-price policy is maintained.

Parallel trade in medicines is linked to a problem of access, in particular the shortage of medicines. A distributor who receives goods from a manufacturer at a low wholesale price may profitably sell the goods in another country, outside the authorized distribution channel. The manufacturer can limit such parallel imports by raising wholesale prices, but this reduces the vertical efficiency of pricing. When the manufacturer sells its product through an agent (distributor) in a particular country, the manufacturer has an incentive to charge the agent a wholesale price that is low enough to induce a desirable retail price in that market, provided that the manufacturer cannot directly set the retail price. This creates an opportunity for the agent to sell the product profitably in another country without the manufacturer's permission. Without a legal constraint on parallel exports, the combined social surplus in two countries first decreases and then increases the private cost of engaging in parallel imports. Restricting parallel imports always benefits the producer, but may increase or decrease the combined social surplus in two countries.

At the end of Chapter 2, the responses from the in-depth interview conducted with professionals in the pharmaceutical sector who have expressed their position on various issues in the area of importation and parallel trade of medicines are described. Three respondents answered the questions: respondent 1 is a national manager of a company re-exporting medicines; respondent 2 is the head of a national agency working in the field of medicine trade in Bulgaria; respondent 3 is a doctor and medical representative in a leading pharmaceutical company (licensed importer of medicines) operating on the Bulgarian market, as well as a representative of a national doctors' organization. The answers of the respondents are systematized in the dissertation.

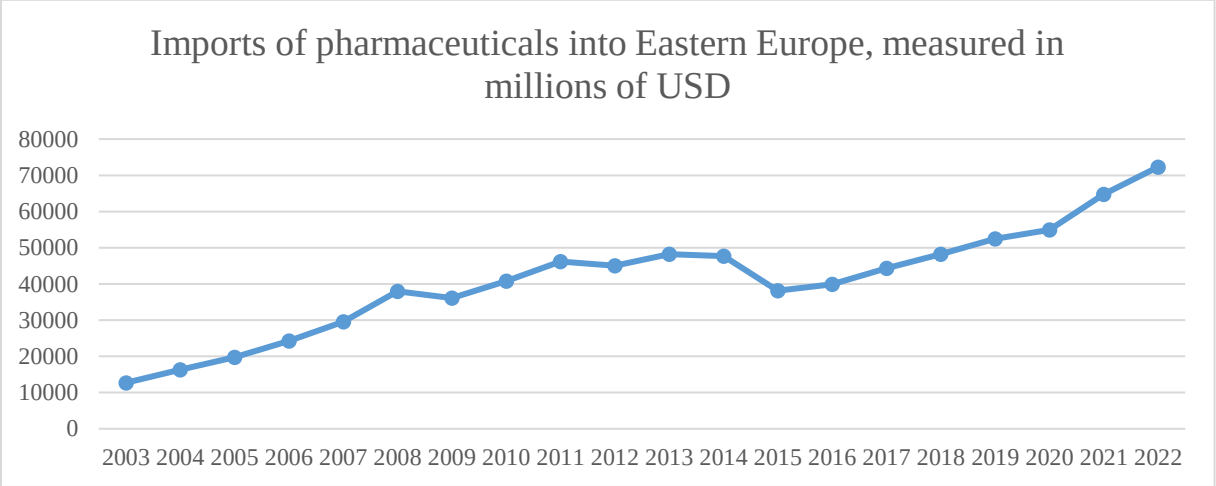
As a summary of the responses, it can be argued that they hold the same views on most of the questions asked. The exception is the case related to whether exports are the reason for the persistent shortage of medicines in Bulgaria. Respondent 1 says on this topic that exports are unregulated, which in practice allows the free export of medicines from Bulgaria to foreign markets. Consequently, warehouses would prefer not to hold stock for a long period of time and could export in order to realise higher profits. Respondent 1 goes on to argue that the measures at State level consist in introducing an export ban list only when the problem of shortages is already present. Therefore, this mechanism does not work to prevent, but rather to minimise the negative effects resulting from drug shortages. The process is as follows: the EMA signals a shortage of medicines. Then, on the basis of Article 217c, para. In accordance with Article 217(7) of the MHMP Act, medicinal products included in the list of the CEPPA (Specialised Electronic Tracking and Analysis System) cannot be exported for the period for which they are listed. A specialised electronic system for tracking and analysis of medicinal products included in the Positive Medicines List is designed to collect information on quantities of medicinal products supplied and dispensed/sold in the country. Based on the information collected, the system will automatically generate a list of medicinal products for which a shortage has been identified. Medicinal products included in this list are prohibited for export abroad. According to respondent 2 and 3, the shortage of certain medicines in the country is due to overconsumption and distortion of medicine use in the country. Moreover, they said, the problem was rooted in import inflexibility rather than excessive exports. This issue is causing controversy among industry organizations, pharmacy owners and warehouses. Recommendations for potential solutions and activities to address the problem of drug shortages are presented after chapter three of the development.

Chapter Three : Analysis and validation of the research hypotheses. Recommendations for improving international import practices of medical companies in crisis settings

The first part of chapter three discusses the scope, objectives and data sources of the empirical study. The international activity of pharmaceutical companies operating in EU markets is a highly complex and multifaceted process that exists and adapts according to EU legislation. Every stage of the research, development, manufacturing, storage and distribution of products (as well as of all active pharmaceutical ingredients) must be carried out in accordance with the applicable internal and external company standards. In every process of these companies, a lot of data, defined as 'confidential information', is accumulated. For the purpose of the study, a written request was made to a large number of pharmaceutical companies operating on the Bulgarian market (manufacturers; importers; intermediaries) to provide information on data on the sales of their products on the Bulgarian market. A categorical refusal was received from the companies to provide information on the quantitative and financial performance of their activities on the Bulgarian market, arguing that this is confidential information which they cannot provide for the purpose of this work. Some of the requests remained unanswered. This circumstance made it necessary to look for other sources of data to make the analysis possible. The study used and referred to a variety of information sources. *The first source used was the company IQVIA, which is a leading global provider of integrated healthcare information and technology services dedicated to helping its clients improve their clinical, scientific and commercial outcomes. The second source used for the study was data provided by the Customs Agency. The third source is the trademap.org website. The fourth source is the Passport database, which is Euromonitor International's market research database.*

The analysis of the data starts with the import of medical products according to Bulgaria's largest trading partners for the period 2003-2022. Some of Bulgaria's largest trading partners for medical products are Hungary, Germany, the Netherlands, Switzerland, Slovenia, Austria, France and Ireland. Data on imports of medical products from the UK are also included in the analysis to check whether Brexit has an impact on imports of medical products into Bulgaria. The data in the thesis is presented in tabular form and the results of medical product imports into Bulgaria from each trading partner are illustrated through figures. The analysis is carried out to confirm or reject Hypothesis 1: Imports of medical products into Bulgaria have grown significantly since Bulgaria joined the EU. As a consequence of reviewing the trends of the data obtained, it can be firmly concluded that imports of medical products into Bulgaria have been growing significantly since the country acceded to the EU. Hypothesis 1 is therefore confirmed. For a more comprehensive analysis, the study also observes the trend of pharmaceutical imports in Eastern Europe. Imports of pharmaceutical products into Eastern Europe, measured in millions of USD, for the same period-2023-2022. The trend in imports into Eastern Europe is also telling - the data show that imports of medical products are increasing many times compared to 2003.

Figure 1: Imports of pharmaceuticals into Eastern Europe, measured in millions of USD



Източник: Passport, Euromonitor International's database

The chapter continues with an analysis of data on imports of antibiotics and vaccines from third countries for the period 2002-2021. For the purpose of the elaboration, the import data of medicines classified under the EU CN are considered as follows:

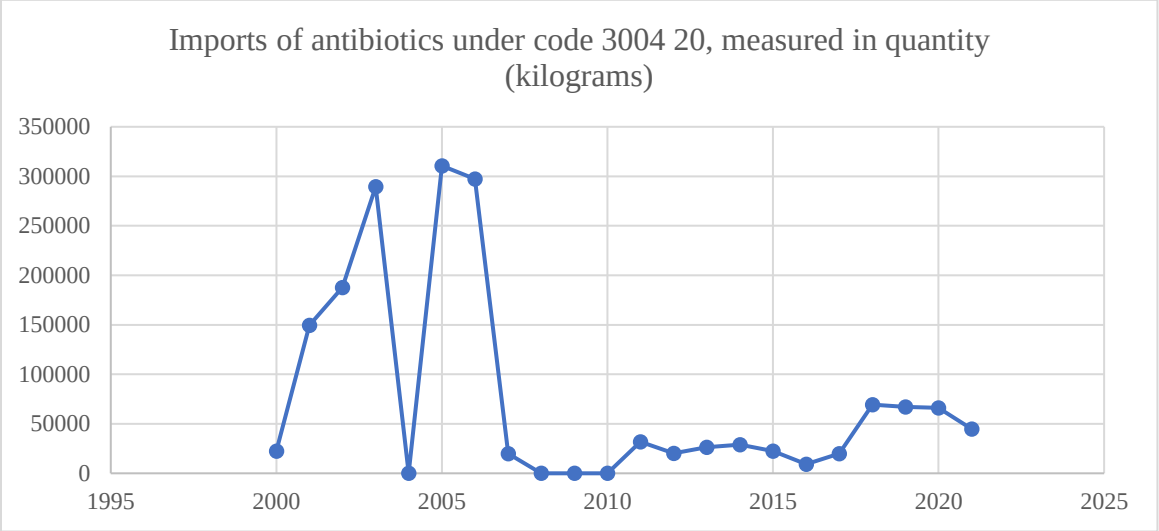
3004 10 - Containing penicillin or derivatives thereof having a penicillinic acid structure, or streptomycins or derivatives thereof;

3004 20- Other, containing antibiotics;

3002- Human blood; animal blood prepared for therapeutic, prophylactic or diagnostic uses; antisera, other blood fractions and immunological products, whether or not modified or obtained by biotechnological means; vaccines, toxins, cultures of micro-organisms (excluding yeasts) and similar products; cell cultures, whether or not modified.

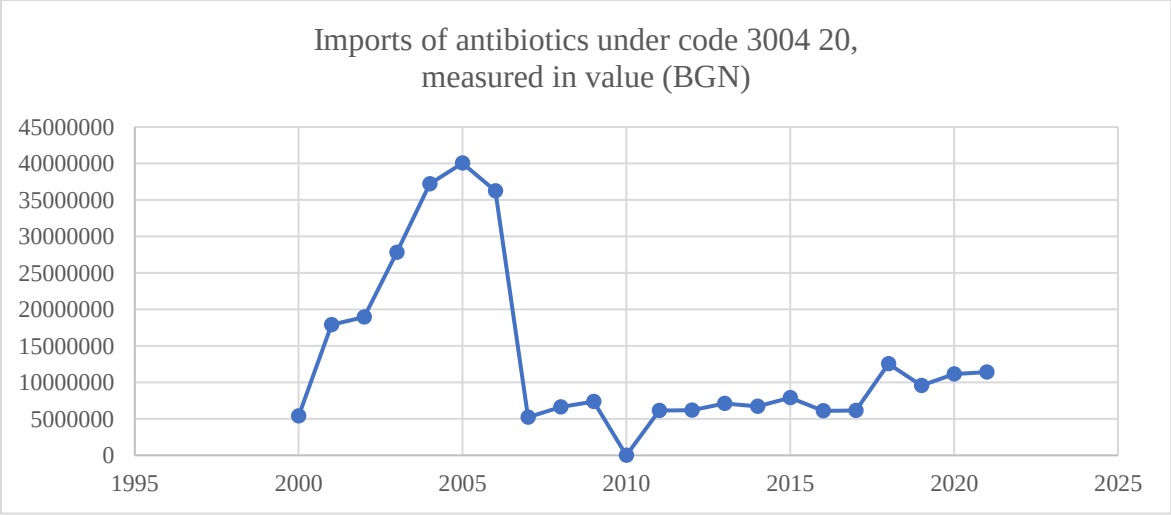
The focus of the study is on the total volume of imported antibiotics (code 3004 20) and the total volume of imported vaccines (code 3002). The quantities are measured in kilograms and the value in Bulgarian leva.

Figure 2. Imports of antibiotics under code 3004 20, measured in quantity (kilograms)



Source:Customs Agency

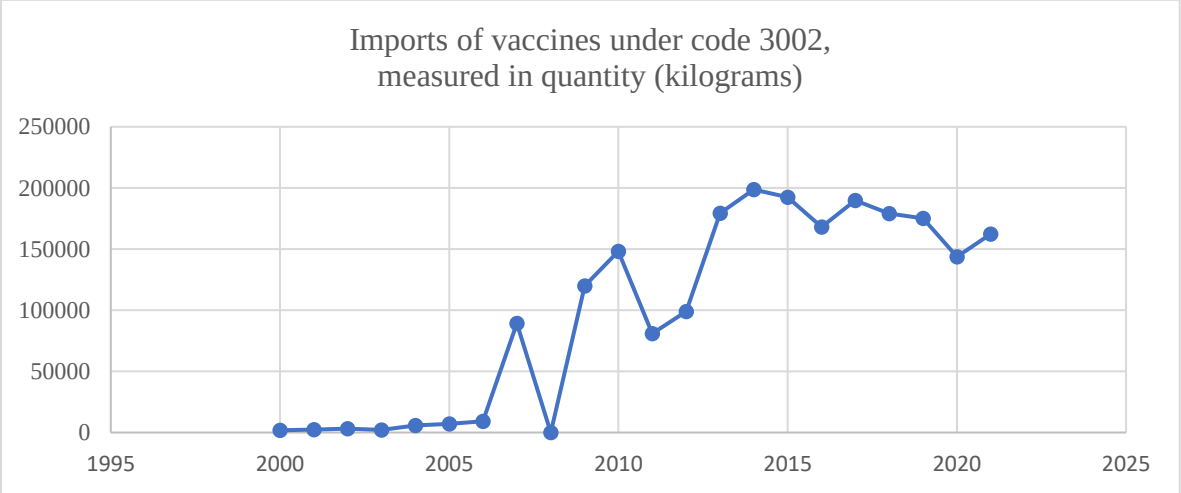
Figure 3. Imports of antibiotics under code 3004 20, measured in value (BGN)



Source:Customs Agency

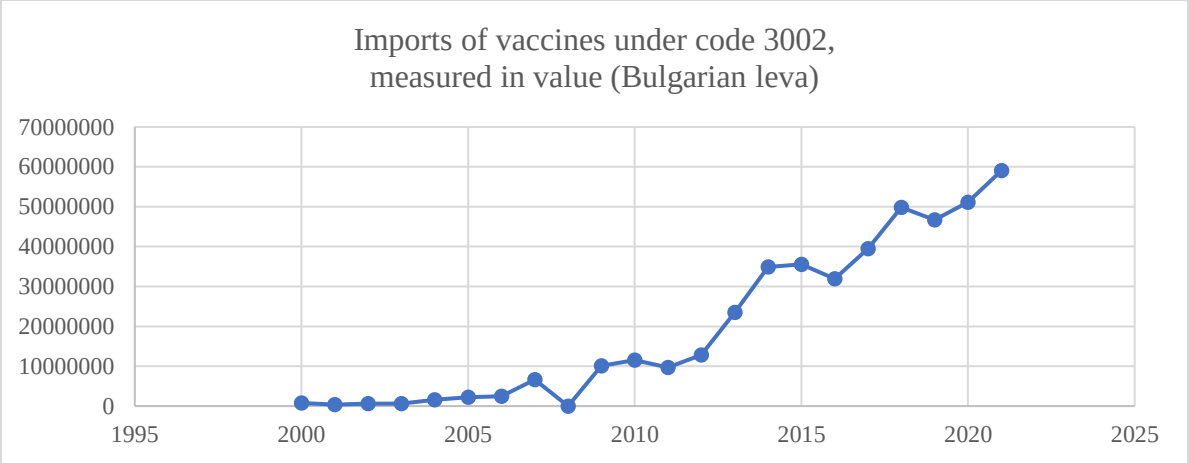
The results that show a trend in the import of drugs from third countries is telling. The conclusion is that after Bulgaria's accession to the EU, the import of antibiotics from third countries has sharply decreased, both in quantitative and value terms. As the Customs Agency does not provide data on imports of antibiotics from third countries for 2010, the level for the year shows '0'.

Figure 4. Imports of vaccines under code 3002, measured in quantity (kilograms)



Source:Customs Agency

Figure 5. Imports of vaccines under code 3002, measured in value (Bulgarian leva)

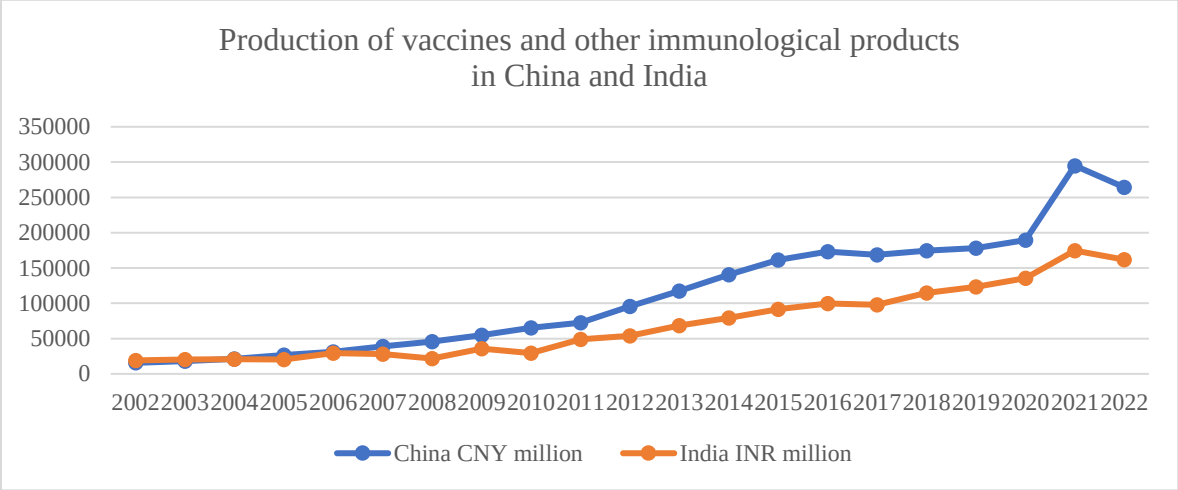


Source:Customs Agency

In contrast to the import of antibiotics from third countries, the data show that for vaccine imports, the trend is reversed. For vaccine imports from third countries, there has been a several-fold increase in both quantitative and value terms since 2007.

The data, which illustrate a significant surge in vaccine imports after 2007 in Bulgaria, prompted the authors to find information on which countries account for the bulk of vaccine production. As indicated in Chapter 1 of the paper, the largest vaccine producers are China and India. Figure 6 shows the growth of vaccine production in the two countries for the period 2002-2022, measured in millions of Chinese yuan and millions of Indian rupees, respectively.

Figure 6: Production of vaccines and other immunological products in China and India

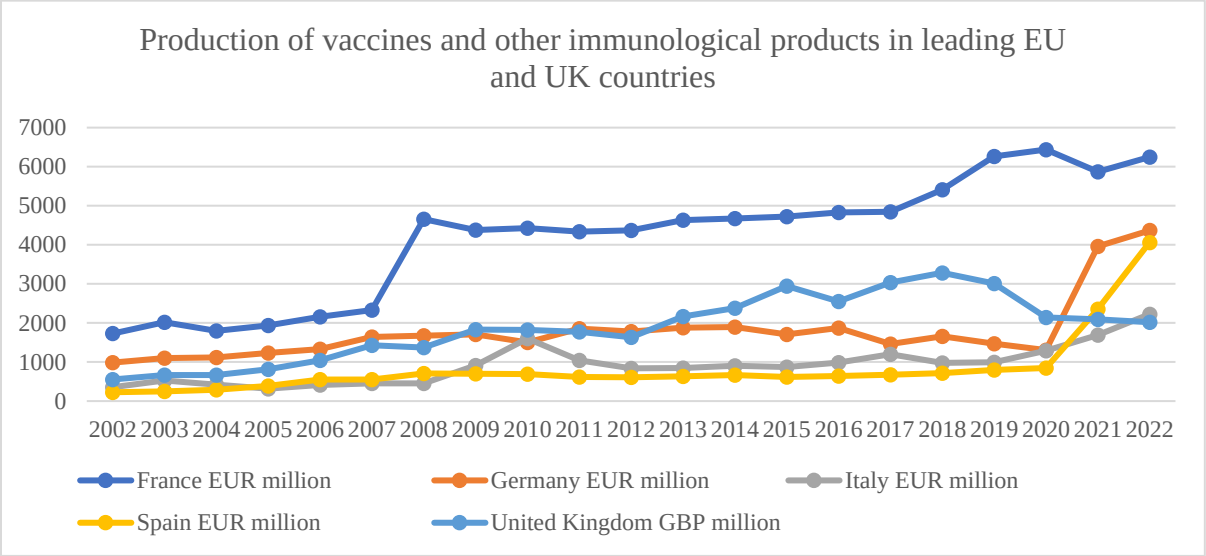


Source: Passport, Euromonitor International's database
(1 EUR=7,70 CNY; 1EUR=88,97 INR); (1USD= 7,24 CNY; 1USD =83,61 INR)

In addition to the multiple growth in vaccine and immunological product production in both countries, there is a significant jump in production from 2020 (the advent of COVID-19) to 2021. The data demonstrates both countries' solid positions in terms of vaccine and immunological product production and their ability to cope with increased demand in a period of increased demand.

To make a comparison with the leading vaccine producers in Europe, data on the production of vaccines and immunological products in the largest representatives of the pharmaceutical industry on the continent - France; Germany; Italy, and Spain - are also presented. Although the UK is not a member of the EU as of January 2020, it is included in the study as a country with a huge presence in the pharmaceutical sector.

Figure 7: Production of vaccines and other immunological products in leading EU and UK countries



Source: Passport, Euromonitor International's database
(1EUR=0,85GPB)

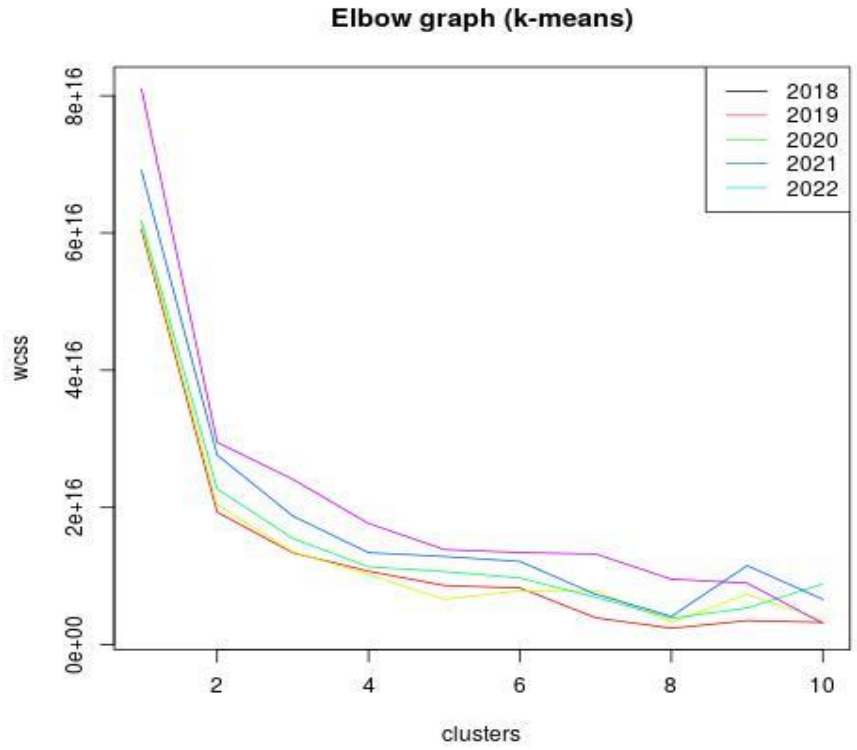
Even taking into account the difference in currency terms of the data presented, the advantage of Asian countries over European countries in terms of vaccine production is clear. Another curious trend that emerges is that all four European countries see significant growth in vaccine and immunology production from 2020 to 2022. The period coincides with the COVID-19 pandemic, indicating the adaptation of production processes in the above countries to meet the increased demand for vaccines in the EU. Significantly, of the 5 countries listed, only UK production shows a decline from 2020 to 2022. This period coincides with both the COVID-19 crisis and the country's exit from the EU.

The analysis continues by examining data on the activities of international companies for the period 2018-2022. IQVIA provides information on direct and parallel imports of medicines and antibiotics into the country by importing companies, as well as the realisation of manufactured medicines in the country, with the dynamics of imports examined through cluster analysis. The results should confirm or reject Hypothesis 2.

Hypothesis 2: The Covid-19 pandemic has an impact on the realization of drug supply in the country. First, data on all medicines that are imported in parallel as well as their equivalents in the market are examined. The cluster analysis starts with data formatting. There are 38 firms in total: ANGELINI ;AS CALCEKS ; ASPEN; ASTRAZENECA; BAUSCH HEALTH; BAYER; BESTAMED; BIOCODEX; BOEHRINGER I; CHEPLAPHARM; CHIESI FARMACEUTI; ECOPHARM EN; GEDEON RICHTER; INNOTHERA; JOHNSON&JOHNSON; KRKA; LUNDBECK; MENARINI ; MERCK KGAA NOVARTIS; ORGANON; PFIZER; PHARMALAKE; PHOENIX; POLPHARMA; RECKITT BENCKISER ; ROCHE DIAGNOST ; SANOFI-AVENTIS; SERVIER; STADA; SWIXX BIOPHARMA; TEVA; UCB; UNIPHARMA BG; US PHARMACIA; VIATRIS; WORWAG PHARMA; ZENTIVA). They are calculated on two amounts - on originator products and on generic products. The amounts are aggregated. Then, for the clustering, the sum original products is used for one coordinate and the sum generic, for the other coordinate, respectively for each company. The clustering is processed for each year separately. The sums cannot be presented as data in the paper because of the contract that obliges the author not to share confidential information.

Clustering is performed on the data from the two tables. - for each of the years- separately. First, we apply the k-means method by running experiments with different numbers of clusters - from 1 to 10. Elbow graph (k-means) - "The elbow method" helps us to find the optimal number of clusters.

Figure 8. Elbow type graph for finding the optimal number of clusters, when analyzing the data for "Original and generic medicines that are imported in parallel, catcato and their equivalents on the market", applying k-means clustering.



Source: author's calculations

This method detects a change in the intra-cluster sums of squares (WCSS) - the so-called "elbow" type graph - looking for where there is a change, a "kink" in the graph, that is the optimal number of clusters. In this case, for two of the years (2020 and 2021) this is at 4 clusters, and for three of the years (2018, 2019, 2022) it is at 5 clusters. The change in the number of clusters itself shows that there is a difference before/after and during the pandemic (i.e. a change in the market structure expressed as generic and originator products).

Having broken down the 10 clusters, we next look at what the clusters themselves are and whether they differ, depending on which firm falls into which cluster, year by year. In order to be able to compare the results, year by year, we apply clustering by 5 clusters, although for 2020 and 2021 the optimal number of clusters is 4 (which actually indicates the impact of the Covid-19 crisis). The distribution over clusters by k-means is reported in Table 2.

Table 2. Distribution of firms by clusters using k-means

Firm	2018	2019	2020	2021	2022
ANGELINI	1	4	1	2	3
AS KALCEKS	4	5	5	1	1
ASPEN	4	5	5	1	1
ASTRAZENECA	4	5	5	1	1
BAUSCH HEALTH	4	1	2	1	2
BAYER	1	4	1	5	3
BESTAMED	2	4	1	2	4
BIOCODEX	4	5	5	1	1
BOEHRINGER I	2	4	5	5	1
CHEPLAPHARM	4	5	5	1	1
CHIESI FARMACEUTI	4	5	5	1	1
ECOPHARM BG	4	5	5	1	1
GEDEON RICHTER	5	2	3	4	4
INNOTHERA	4	5	5	5	1
JOHNSON&JOHNSO N	2	4	5	5	3
KRKA	3	1	2	3	2
LUNDBECK	4	5	5	5	1
MENARINI	5	2	3	4	4
MERCK KGAA	3	3	4	3	5
NOVARTIS	3	3	4	3	5
ORGANON	4	5	5	5	1
PFIZER	4	5	5	1	1
PHARMALAKE	4	5	5	5	3
PHOENIX	5	2	3	2	4
POLPHARMA	4	5	5	1	1
RECKITT BENCKISER	2	4	1	2	2
ROCHE DIAGNOST	4	5	5	5	1
SANOFI-AVENTIS	4	5	5	1	1

SERVIER	3	3	4	3	5
STADA	3	1	2	1	2
SWIXX BIOPHARMA	2	4	1	5	1
TEVA	2	5	1	5	1
UCB	1	4	1	2	3
UNIPHARMA BG	2	4	5	5	3
US PHARMACIA	4	5	5	1	1
VIATRIS	5	2	3	4	4
WORWAG PHARMA	2	4	1	5	3
ZENTIVA	3	1	2	1	2

Source: author's calculations

Following the clustering presented in the table, we check whether the clusters are interchanged across years - whether the same firm is in the same cluster (in the same group with well-defined other firms or not). In other words, whether they remain clustered together over the years or not. It is done with a test that uses the Rand index, which takes values from 0 to 1. The closer the coefficient is to 1, the less the difference between groupings by cluster. The results found are illustrated in Table 3:

Table 3. Results of Rand index grouping

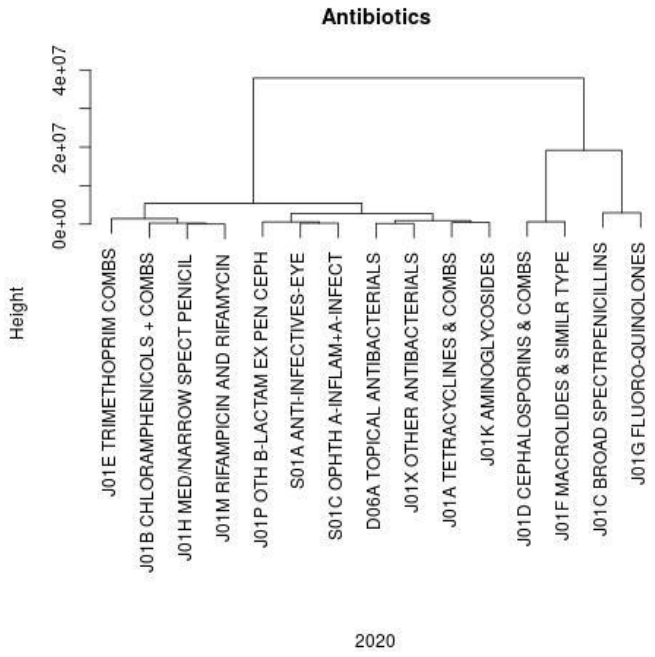
Year	Rand index
2018/2019	0.898
2019/2020	0.869
2020/2021	0.741
2021/2022	0.745

Source: author's calculations

Again, the result obtained with the Elbow plot is confirmed, namely that there is a significant change in clustering before and after the pandemic. The results show that Covid- 19 significantly restructured the market.

To illustrate the clustering, a figure was developed that illustrates the clustering of antibiotics for the year 2020.

Figure 9. Illustrative clustering of antibiotic groups, for the year 2020, applying hierarchical clustering.



Source: author's calculations

The different types of antibiotics are clustered according to the data obtained. Whether or not they correlate to parallel imports are used as the coordinates. For each antibiotic type, a sum at k-means is calculated, which results are presented in the table below.

Table 4. Import amounts by antibiotic code reflected in the 10 clusters for the period 2018-2022

	2018	2019	2020	2021	2022
1	1.89e+15	1.92e+15	2.35e+15	2.99e+15	3.19e+15
2	2.64e+14	2.51e+14	3.49e+14	5.40e+14	6.31e+14
3	1.23e+14	1.19e+14	3.17e+14	1.53e+14	2.26e+14
4	9.26e+13	9.07e+13	1.31e+13	1.06e+14	1.80e+14
5	1.70e+13	1.43e+13	6.69e+12	9.98e+13	1.61e+14
6	5.87e+12	8.12e+13	5.33e+12	9.80e+13	3.56e+13
7	7.90e+13	7.88e+13	9.59e+11	9.73e+13	1.57e+14
8	7.87e+13	2.46e+12	5.14e+12	1.13e+12	3.22e+13
9	7.73e+13	1.74e+12	4.66e+12	9.87e+13	3.18e+13

10	7.69e+13	7.81e+13	2.90e+11	9.71e+13	1.57e+14

Source: author's calculations

The data shows that the optimal number of clusters by year 2018; 2019; 2020; 2021 and 2020 is 3; 3; 4; 3; and 3 respectively. For the year 2020, again there is an anomaly compared to the other years.

This time, when comparing the composition of the clusters, a split into 3 clusters is applied for all years.

Table 5: Distribution of antibiotic types by clusters using k-means

Код антибиотик	2018	2019	2020	2021	2022
D06A TOPICAL ANTIBACTERIALS	2	3	1	2	2
J01A TETRACYCLINES & COMBS	2	3	1	2	2
J01B CHLORAMPHENICOL + COMBS	2	3	3	1	2
J01C BROAD SPECTRPENICILLINS	3	2	2	3	3
J01D CEPHALOSPORINS & COMBS	3	2	2	3	1
J01E TRIMETHOPRIM COMBS	2	3	3	1	2
J01F MACROLIDES & SIMILR TYPE	3	2	2	3	1
J01G FLUORO-QUINOLONES	1	1	2	3	3
J01H MED/NARROW SPECT PENICIL	2	3	3	1	2
J01K AMINOGLYCOSIDES	2	3	1	2	2
J01M RIFAMPICIN AND RIFAMYCIN	2	3	3	1	2

J01P OTH B-LACTAM EX PEN CEPH	2	3	1	2	2
J01X OTHER ANTIBACTERIALS	2	3	1	2	2
S01A ANTI-INFECTIVES-EYE	2	3	1	2	2
S01C OPHTH A-INFLAM+A-INFECT	2	3	1	2	2

Source: author's calculations

After the clustering presented in the table, again a check is made on whether the clusters are interchanged over the years - whether or not the same group of antibiotics is in the same cluster (in the same group) with precisely defined other groups of antibiotics). Whether they remain grouped over the years or not. The results found are illustrated in the following table:

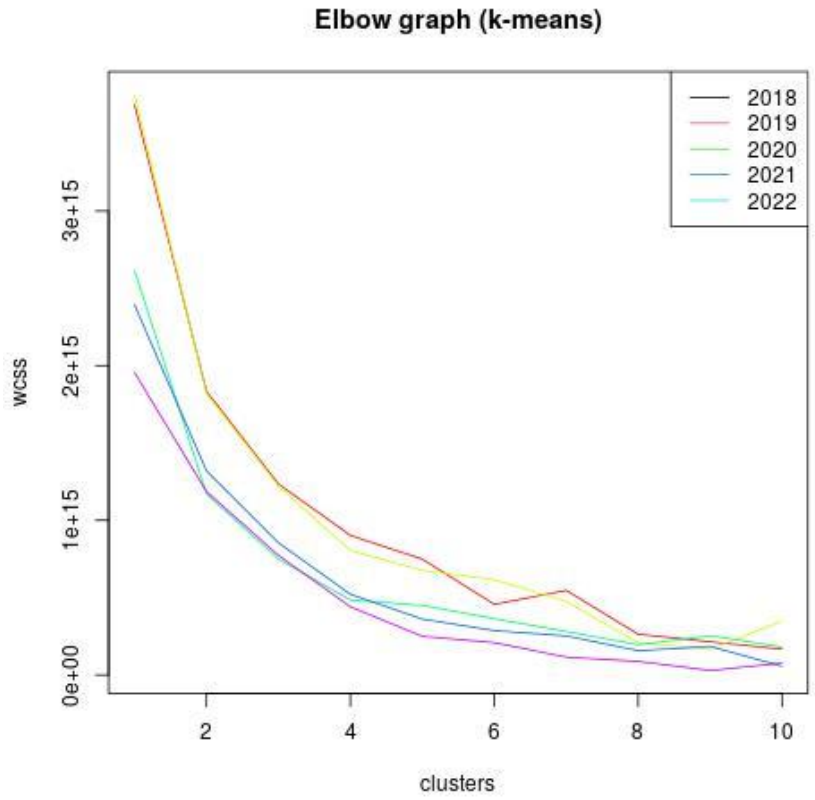
Table 6: Results of grouping antibiotics by Rand index

Year	Rand index
2018/2019	1
2019/2020	0.7
2020/2021	1
2021/2022	0.695

Source: author's calculations

Similarly, the analysis of products by manufacturers in the Bulgarian market is carried out. For the purpose of the analysis, a distinction is made between originator and generic medicines, as well as antibiotics and non-antibiotics. The companies are classified, which number 36. The analysis starts by checking the optimal number of clusters.

Figure 10. Elbow-type plot for determining the optimal number of clusters, when analyzing products by manufacturer, when applying k-means clustering.



Source: author's calculations

The specific figures for these amounts are reflected in Table 7.

Table 7: Amounts by product of producers reflected in the 10 clusters for the period 2018-2022

	2018	2019	2020	2021	2022
1	3.69e+15	3.75e+15	2.62e+15	2.39e+15	1.96e+15
2	1.83e+15	1.82e+15	1.17e+15	1.32e+15	1.19e+15
3	1.23e+15	1.22e+15	7.48e+14	8.55e+14	7.73e+14
4	9.02e+14	8.04e+14	4.85e+14	5.21e+14	4.40e+14
5	7.48e+14	6.76e+14	4.50e+14	3.61e+14	2.50e+14
6	4.56e+14	6.16e+14	3.63e+14	2.86e+14	2.09e+14
7	5.47e+14	4.76e+14	2.81e+14	2.52e+14	1.15e+14
8	2.63e+14	2.08e+14	1.95e+14	1.57e+14	8.75e+13
9	2.14e+14	1.66e+14	2.54e+14	1.84e+14	2.85e+13

10	1.67e+14	3.48e+14	1.81e+14	5.62e+13	7.69e+13

Source: author's calculations

From the stage of defining the clusters for each year, the following distributions are available: for 2018, the optimal number of clusters is 6; for 2019, 4 clusters; for 2020, 4 clusters; for 2021, 5 clusters; for 2022, 5 clusters. We choose to allocate by 5 clusters, again using a k-means method.

Table 8: Clustering of producers by k-means reflected in the 10 clusters, 2018-2022

Firm	2018	2019	2020	2021	2022
ANGELINI	5	4	5	2	5
AS KALCEKS	5	4	5	2	5
ASPEN	5	4	5	2	5
ASTRAZENECA	2	4	5	2	5
BAUSCH HEALTH	3	1	1	1	2
BAYER	2	1	2	3	4
BIOCODEX	5	4	5	2	5
BOEHRINGER I	5	4	5	2	5
CHEPLAPHARM	5	4	5	2	5
CHIESI FARMACEUTI	5	4	5	2	5
ECOPHARM BG	5	4	5	2	5
GEDEON RICHTER	1	5	4	4	1
INNOTHERA	5	4	5	2	5
JOHNSON&JOHNSON	2	1	2	3	4
KRKA	5	4	5	2	5
LUNDBECK	5	4	5	2	5
MENARINI	3	4	5	5	5
MERCK KGAA	5	4	5	2	5
NOVARTIS	2	4	5	2	5
ORGANON	2	4	5	2	5
PFIZER	5	4	5	2	5
PHOENIX	5	2	4	2	5
POLPHARMA	5	4	5	2	5
RECKITT BENCKISER	2	4	2	5	3
ROCHE DIAGNOST	5	4	5	2	5
SANOFI-AVENTIS	5	4	5	2	5
SERVIER	1	5	2	5	5

STADA	3	1	1	1	5
SWIXX BIOPHARMA	2	1	3	3	2
TEVA	2	1	3	3	2
UCB	5	4	5	2	5
UNIPHARMA BG	5	4	5	3	5
US PHARMACIA	5	4	5	2	5
VIATRIS	4	3	3	1	2
WORWAG PHARMA	2	1	2	3	4
ZENTIVA	2	1	5	2	5

Source: author's calculations

Again, a check is performed to match the clusters with the Rand index.

Table 9. Results of the clustering of products by manufacturers according to the Rand index

Year	Rand index
2018/2019	0.75
2019/2020	0.87
2020/2021	0.86
2021/2022	0.82

Source: author's calculations

Producer data also demonstrate a significant change in market structure during the pandemic. Checking for within-cluster totals suggests that the optimal number of clusters is 4, except for the last year. Therefore, the study continues with 4 clusters included.

Table 10. Clusters of producers under hierarchical clustering

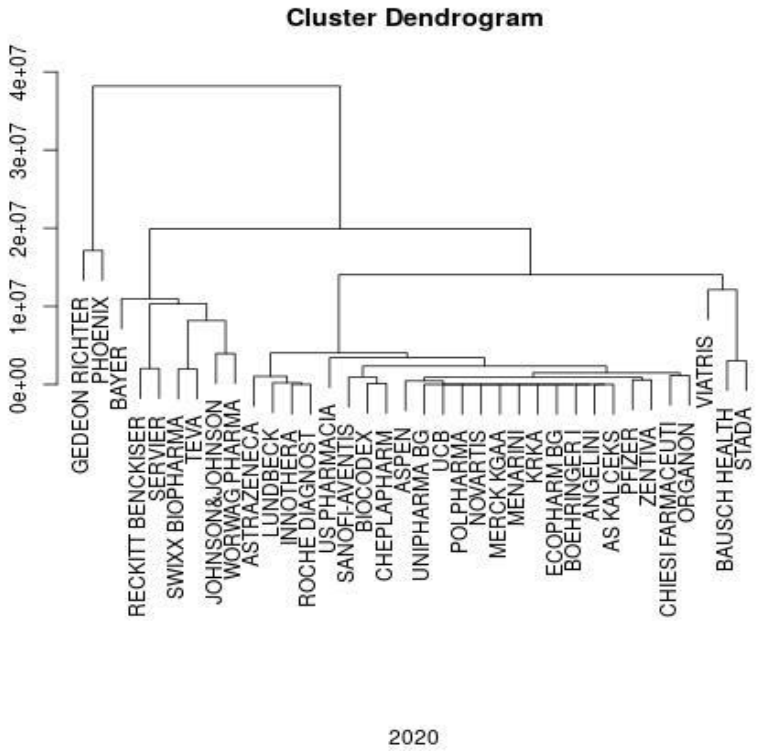
Firm	2018	2019	2020	2021	2022
ANGELINI	1	1	1	1	1
AS KALCEKS	1	1	1	1	1
ASPEN	1	1	1	1	1
ASTRAZENECA	1	1	1	1	1
BAUSCH HEALTH	2	2	2	2	1
BAYER	1	2	3	3	2
BIOCODEX	1	1	1	1	1
BOEHRINGER I	1	1	1	1	1
CHEPLAPHARM	1	1	1	1	1
CHIESI FARMACEUTI	1	1	1	1	1

ECOPHARM BG	1	1	1	1	1
GEDEON RICHTER	3	3	4	4	3
INNOTHERA	1	1	1	1	1
JOHNSON&JOHNSON	1	2	3	3	2
KRKA	1	1	1	1	1
LUNDBECK	1	1	1	1	1
MENARINI	1	1	1	5	1
MERCK KGAA	1	1	1	1	1
NOVARTIS	1	1	1	1	1
ORGANON	1	1	1	1	1
PFIZER	1	1	1	1	1
PHOENIX	1	1	5	1	1
POLPHARMA	1	1	1	1	1
RECKITT BENCKISER	1	1	3	3	4
ROCHE DIAGNOST	1	1	1	1	1
SANOFI-AVENTIS	1	1	1	1	1
SERVIER	4	4	3	3	1
STADA	2	2	2	2	1
SWIXX BIOPHARMA	1	2	3	3	2
TEVA	1	2	3	3	2
UCB	1	1	1	1	1
UNIPHARMA BG	1	1	1	3	1
US PHARMACIA	1	1	1	1	1
VIATRIS	5	5	2	2	5
WORWAG PHARMA	1	2	3	3	2
ZENTIVA	1	2	1	1	1

Source: author's calculations

Since 2020 coincides with the Covid-19 period, we again report the cluster distribution for 2020, this time illustrated by a cluster dendrogram.

Figure 11. Cluster dendrogram for 2020



Source:Author

Table 11. Results of Rand index grouping of products by manufacturers (4 clusters)

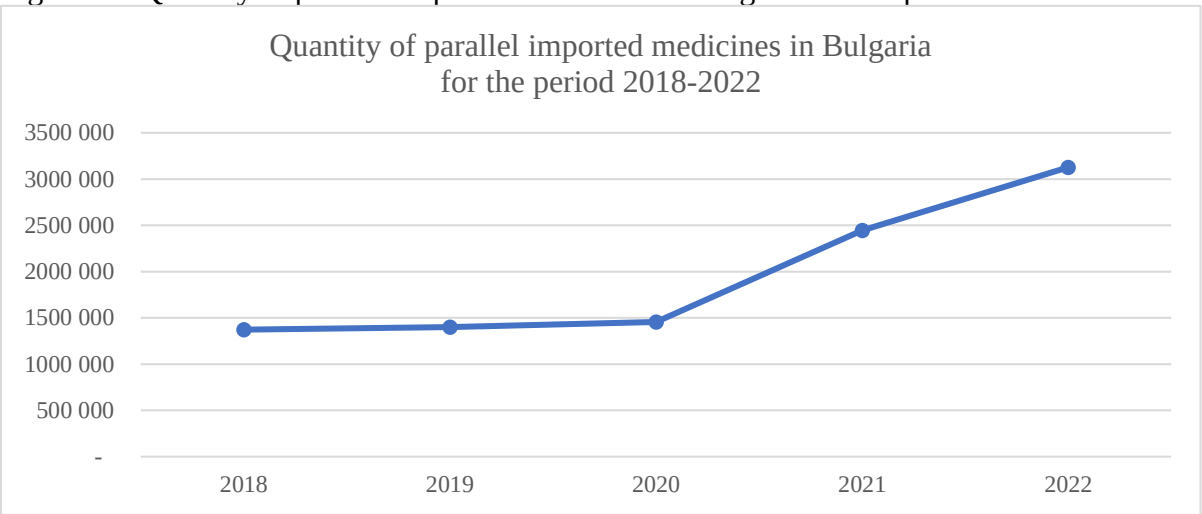
Year	Rand index
2018/2019	1
2019/2020	0.65
2020/2021	0.55
2021/2022	0.80

Source: author's calculations

As a result of the cluster analysis conducted to confirm or reject hypothesis 2, which states that the Covid-19 pandemic has an impact in the realization of drug supply in the country, it can be concluded that the objective has been achieved and the hypothesis has been confirmed.

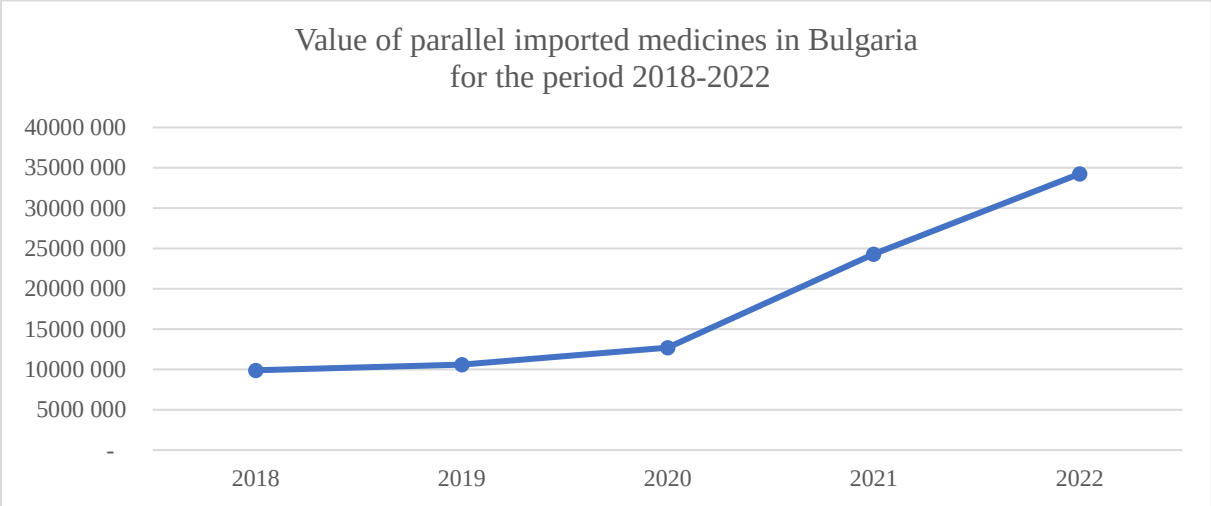
The third chapter continues by examining the trends in parallel import and import of generic medicines for the period 2018-2022. The aim of the analysis is to confirm or reject Hypothesis 4 of the study, which states that the import of generic medicines in Bulgaria has a significant growth for the study period 2018-2022.

Figure 12. Quantity of parallel imported medicines in Bulgaria for the period 2018-2022



Source: IQVIA

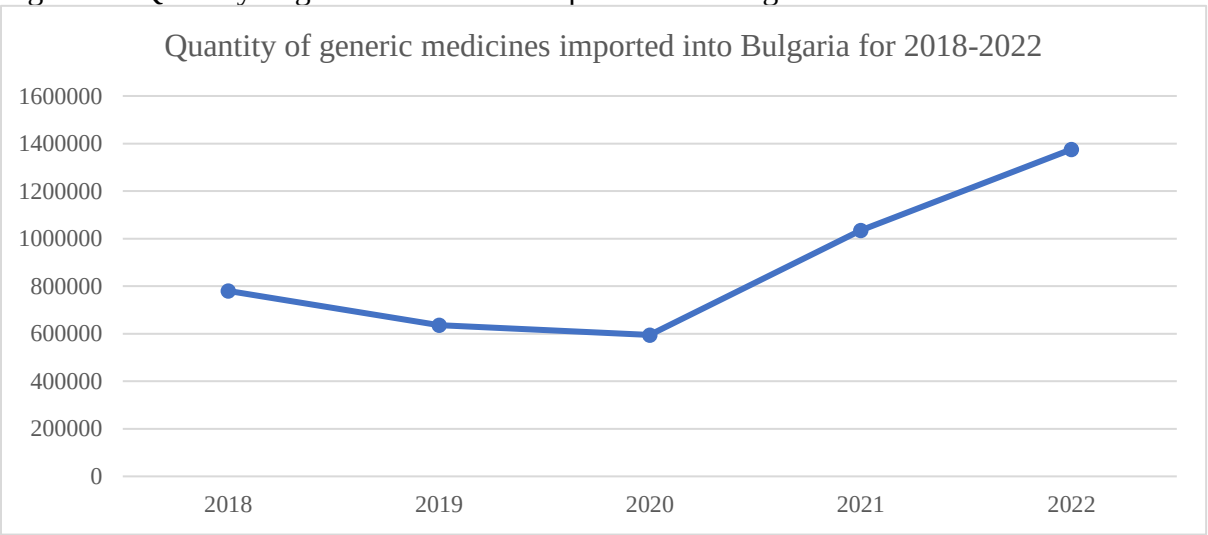
Figure 13. Value of parallel imported medicines in Bulgaria for the period 2018-2022



Source: IQVIA

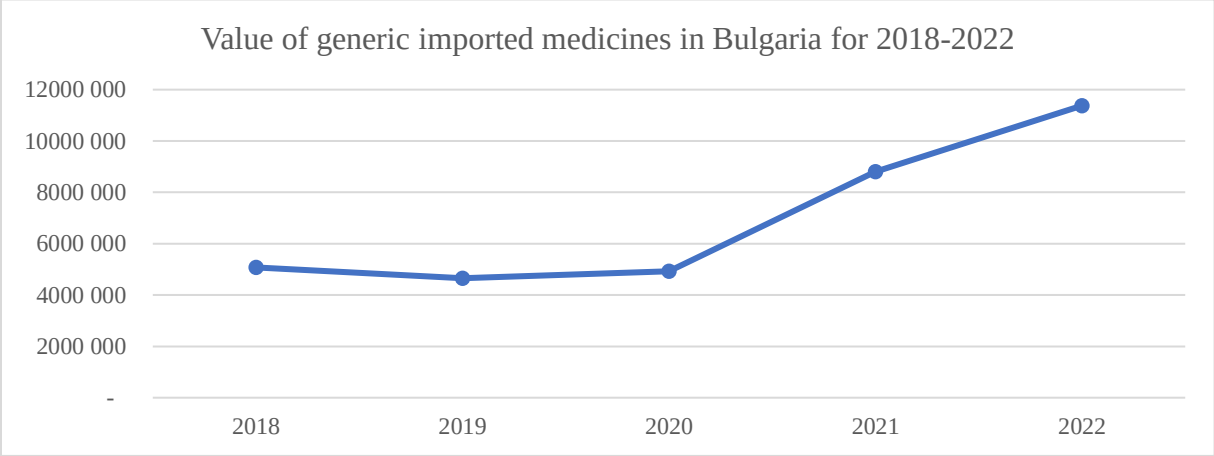
The levels of parallel imported medicines in Bulgaria remain constant until 2020, after which imports will see a sharp increase. There is a threefold increase in the quantities of medicines imported in parallel, which is also indicative of the fact that parallel imports are strengthening their position in supplying the Bulgarian market with medicines.

Figure 14. Quantity of generic medicines imported into Bulgaria for 2018-2022



Source: IQVIA

Figure 15. Value of generic imported medicines in Bulgaria for 2018-2022



Source: IQVIA

Similar to the results observed for parallel imports, the figures show that generic imports in 2020 remained relatively constant compared to the previous two years. It is interesting to note, however, that generic imports in 2022 increase threefold in quantity and value relative to 2020. Hence, we can conclude that hypothesis 4, which states that the import of generic medicines in Bulgaria has a significant growth for the study period 2018-2022, is validated.

Key findings and conclusions:

Finding 1: EU Member States are responsible for developing health policies and for the provision of health products and medical care. The EU has complementary competences that allow it to support and coordinate action and to adopt binding legislation on medicines and medical devices. Since 2007, Bulgaria has been part of the EU, which has to implement concrete measures to ensure the availability of medicines, as well as to engage in shortage management within the Union. Medicines for human use must meet strict authorisation procedures to prove that they meet high quality and safety standards. In conjunction with these rules, the various national regulations must also be removed to ensure that medical and medicinal products are available throughout the European Union (EU) and to ensure that markets are secured. There is

a mutual recognition procedure to enable medicines already authorized in one EU country to be sold in another. Furthermore, it should be borne in mind that globalization has made supply chains more complex. EU regulations respond to this by trying to streamline the process by classifying importers of medicines as manufacturers, requiring them to obtain a Manufacturing Authorisation (MA), thus providing a regulatory framework to deal with this situation. As MIA holders, importers are required to comply with Good Manufacturing Practice (GMP) requirements, such as: establishing a quality system for pharmaceutical products, being able to have sufficient staff and premises for the activities in question, taking appropriate measures to manage complaints and recalls of medicines, implementing supply chain control procedures. On the other hand, the European Parliament has consistently promoted the creation of a coherent public health policy and a pharmaceutical policy that would take into account both the public health interest and industrial aspects. Bulgaria can count on support for long-term security of supply, as action against shortages of medicines should be coordinated within the Union and supply chain vulnerabilities addressed.

Conclusion 2: Managing pharmaceutical supply chains in times of crisis becomes more complex because it involves the life-saving interest of people and requires the involvement of various stakeholders such as pharmaceutical manufacturers, wholesalers, distributors, customers, information service providers, and regulatory agencies. In addition, this year the local economy must adapt quickly to specific population needs in a short period of time. The changes in these processes in the year of Covid-19 can on the one hand be attributed primarily to the influence of China as one of the significant factors in the production and distribution of medical products and medicines. Mainly a small number of pharmaceutical manufacturing plants based in China and India supply the world with the majority of active pharmaceutical ingredients (APIs). Should a surge in demand from Europe or elsewhere occur, this puts a strain on those manufacturers who still have limited production capacity. If manufacturers are also struggling with product quality issues or if their emissions are harmful to the environment, they will face time-consuming plant inspections and potentially even plant closures due to detected violations. These delays also affect the supply chain.

Conclusion 3: Parallel imports have a complementary and competition-ensuring function. The concept of parallel imports cannot guarantee future supplies as required of marketing authorisation holders. Accordingly, projections for parallel imports cannot be made because:

- parallel distributors do not have and cannot have permanent and guaranteed access to medicinal products from other Member States;
- parallel distributors in the European Union rely on temporary and unpredictable stocks and quantities;
- the parallel distributors are not manufacturers, distributors/wholesalers who acquire medicinal products from other European distributors or wholesalers in the EU, i.e. they cannot control the manufacturing process and supply chain of the manufacturers in order to guarantee quantities to supply the relevant markets;
- it is not the case that any parallel importer would be able to predict what the stocks of any product would be, even 3 months in advance, in order to be legally obliged to notify the regulatory authorities within 3 months prior to the discontinuation of sales of a specific medicinal product;
- stocks of medicinal products are regulated and provided for independently by each Member State according to a different model. In this setting, parallel distributors are only distributors of medicinal products in the EU who adapt their activities to the free movement of stocks of medicinal products. They do not have the status of manufacturer or official

representative for a specific Member State and for these reasons there is no justification or legal logic to impose on them identical obligations to those of official representatives and manufacturers of medicinal products.

Scientific contributions in the dissertation work

The dissertation is a topical and innovative research in the field of international activities of the pharmaceutical industry companies in Bulgaria. This statement is supported by the author's contributions, in particular:

1. Based on a comprehensive and in-depth study of theoretical views on the nature of regional integration and the impact of the global world on the development of the pharmaceutical business and its adaptation to the international political, economic, and social environment.

2. In a theoretical and applied aspect, the dissertation explores and proves the key role of the pharmaceutical industry and the dynamics of its development for the well-being of nations. The established propositions and conclusions are also essential in proving the author's thesis and hypotheses through in-depth interviews and data analysis from a variety of sources.

3. The dissertation contributes to expanding the scope of the application of familiar research tools in an under-studied area of international business - the pharmaceutical industry.

4. As a result of the conducted research and analysis, the dissertation provides concrete suggestions to companies and institutions that they could use in the decision-making process regarding the supply of medical products and medicines to the markets, especially in times of crises and unpredictability.

Recommendations

The following recommendations can be made to ensure that the Bulgarian market is supplied with the necessary medicinal products.

In order to guarantee the production processes, stocks of raw materials and ingredients of medicinal products in EU countries should be secured. This will minimise dependence on production facilities in Asian countries and their readiness to supply other continents at any time of need. With the availability of raw materials and ingredients assured, production will be able to take place within Europe, and to meet even increasing demand for medicines in local markets. In addition, manufacturers will be able to supply the necessary quantities of medicinal products to local markets more easily and in shorter timeframes. After the production stage, it is necessary to ensure that medicinal products are stored correctly and according to individual criteria and requirements. The recommendation is oriented towards the provision of storage facilities for medicines and medical products in European Union or EEC countries. At the company level, one of the most common strategies for building supply chain resilience is to expand the supplier network. Reliance on a single supplier for a product group can be a cause of serious vulnerability, as can dependence on multiple suppliers geographically concentrated in the same location. This is where so-called multisourcing, or working in parallel with several suppliers of the same products and substances, ideally based in different locations and shortening the length of supply chains geographically, can provide a solution. Providing such opportunities for flexible reordering and stock optimization is among the arguments in favour of diversification by attracting suppliers and/or building production capacity in Central and South East Europe. Maintaining additional stocks of medicines is also a measure that would secure markets in times of unplanned demand at short notice. Online regulation of supply as well as data on the stock of medicines in a single electronic European network would provide information on quantities in each EU country. If, for example, the medicines dispensed from country X to manufacturer/trader Y for country Z are recorded in this system, real-time tracking of exports and imports respectively would minimise the opportunities for malpractice and reduce unregulated exports. A sustainable pharmaceutical industrial ecosystem in Europe should be fostered by implementing core pharmaceutical business activities. In addition to meeting the need for medicines and medical products, this would stimulate economic growth and employment in Europe.

Regarding parallel trade in medicines, there are certain administrative gaps and obstacles to the effective implementation of parallel imports on the Bulgarian market. Currently, there is no legal possibility for a price notification regime for parallel imported medicines. This price already exists in Bulgaria for the product being parallel imported and should be automatically entered in all NDCMP applications. After the granting of a marketing authorisation for a parallel imported medicinal product by the Executive Agency for Medicinal Products, there remains the 30-day deadline for the National Council for the Pricing and Reimbursement of Medicinal Products to issue a price decision, which is often extended for various administrative reasons. This procedural delay leads to an extension of the time limit for medicines to reach patients. Efficiency and streamlining of the process would be achieved if a notification regime were introduced with automatic validation of the price of parallel imported medicines with that of the original importer. Reducing the administrative burden and streamlining the procedures for obtaining a price and inclusion in the Positive Medicines List would limit the process of over-administration and compliance with acceptable time limits.

IV. Conclusion

The pharmaceutical industry is a sector that has a significant impact on societies, and whose activities can reflect on both the social and economic well-being of nations. In recent decades, there have been significant dynamics in the development of the pharmaceutical business in terms of production, innovation and marketing of medicines. This creates the conditions for increasingly close links and interactions between companies and the countries in which they operate. The activities of pharmaceutical companies are based on a complex web of interconnections and dependencies on supply and production processes, R&D, international trade relations and political-legal regulations. The undeniable importance of the sector requires the necessity of its functioning and the continuity of its activities, even under unpredictable circumstances (e.g. the Covid-19 pandemic). It is the period of the international health crisis and its social and economic consequences that provoked us to examine the specificities of the activities of pharmaceutical companies operating in Bulgaria. The choice of a topic that is topical and still new for researchers, as well as the object of the research - pharmaceutical companies, posed significant challenges.

The main thesis in this dissertation suggests that parallel importation and importation of generics can ensure continuity of supply of medicines to ensure access to medicines by patients in the country. It is based on four hypotheses.

Hypothesis 1: Imports of medical products into Bulgaria have grown significantly since Bulgaria's accession to the EU.

To validate the first hypothesis, a set of sources and data on the import of medicines into Bulgaria for the period 2002-2021 are analyzed. The structure and organization of the pharmaceutical business and trade in medicines in Bulgaria, as well as the responsible authorities that regulate the production and import of medicines in the country after EU accession are detailed. Data on imports of medical products from Bulgaria's largest trading partners are used. As a summary of the evidence from the theory and as a consequence of the review of the trends from the data obtained, it can be concluded that the import of medical products in Bulgaria has grown significantly since the country's accession to the EU. We can therefore conclude that hypothesis 1 is valid.

Hypothesis 2: The COVID-19 pandemic has an impact in the realization of drug supply in the country.

To validate the second hypothesis, an analysis of the impact of COVID-19 on drug supply systems, as well as the opportunities and negative effects provoked by the health crisis, was conducted. A cluster analysis has also been performed, the result of which shows changes in the implementation of the supply of medicines in Bulgaria. We can therefore conclude that hypothesis 2 is validated.

Hypothesis 3: Parallel trade contributes to the supply of missing medicines on the market through imports.

The term "parallel trade" is introduced in the paper and a theoretical review of this type of distribution of medicines in the single market is made. For the purpose of the analysis of the pharmaceutical market activity in Bulgaria, an in-depth interview was conducted with specialists in the pharmaceutical sector to provide clarifications on various issues in the field of

import and parallel trade of medicines. Gaps in the regulatory framework and malpractices in the sector were noted. A threefold increase in the quantities of medicines imported in parallel was noted during the period under review, which is also indicative of the fact that this type of import is strengthening its position in supplying the Bulgarian market with medicines. We can therefore conclude that hypothesis 3 is valid.

Hypothesis 4: Imports of generic medicines in Bulgaria will grow significantly over the study period 2018-2022.

After a theoretical review, definitions of generic medicines are adopted. The increased role of this type of medicines in supplying the markets with medicines is considered. The advantages arising from the possibility of importing generic medicines into the country are systematized, as well as the negative effects that their consumption may lead to. Data on the import of generic medicines in Bulgaria in 2022 in quantitative and value terms increases threefold compared to that of 2020. We can therefore conclude that hypothesis 4 is validated.

In conclusion, the dissertation achieves its objectives, goals and proves the thesis that parallel import and import of generics can ensure continuity of supply of medicines to ensure access to medicines by patients in the country. This validation of the thesis underscores the critical role that parallel importation and generic medicines have in ensuring the supply of needed medical products to markets, especially in a pedestrian environment of unpredictability and increase in demand for medicines. The results obtained and the interpretation of the data open the horizon to other topics to serve future research in the field.

Recommendations are made to pharmaceutical manufacturers and importers, as well as the institutions involved in the field. It is necessary to outline new directions in the development of the international activities of the companies to ensure stability in the import of medicines to ensure the supply of medicines to patients in optimal time.

V. List of publications on the topic of the dissertation:

1. Dobreva, R. Effects on Bulgarian Market from Parallel Trade of Medicines in the EU. The Membership of Bulgaria in the European Union : Thirteen Years Later : Nineteenth International Scientific Conference, 16 October 2020, UNWE - Sofia : Vol. 2, Sofia : UNWE Publ., 2 , 2021, 171-180.

2. Dobreva, R. A Crisis Within the Crisis : The impact of Covid-19 and Brexit On Supply Chains in the Pharmaceutical Industry. IZVESTIYA JOURNAL OF VARNA UNIVERSITY OF ECONOMICS, UE-Varna, 64, 2020, 3, 352-368.

3. Dobreva, R., The impact of Brexit on the countries of Central and Eastern Europe. Scientific Conference : TechCo-Lovech 2019, 10 May 2019 : Proceedings : Vol. 1, Gabrovo : Univ. ed. B. Aprilov, 1, 2019, 189-199.

4. Dobreva, R., Boshnakov, P. The impact of Brexit on the UK pharmaceutical industry. Integration processes in the global economy : International scientific conference dedicated to the 25th anniversary of Cat. MIE, Svishtov, 11 - 12 May 2018 : Proceedings, Svishtov : Acad. ed. Tsenov, 2018, 245 - 251.

The thesis and the abstract are the original work of the author Ralina Dobrinova Mircheva.