Ф А 2.2.1-32-367

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QUALIFICATION WORK

on the topic: **"A STUDY ON THE ORGANIZATION OF PHARMACEUTICAL CARE FOR PATIENTS WITH ORPHAN DISEASES"**

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Kharkiv – 2024 year

ANNOTATION

The qualification work is concerned with the problem of the organisation of pharmaceutical care for patients with orphan diseases.. It presents the results of data analysis to determine the status of orphan diseases and their classification, approaches to diagnosis and treatment, and approaches in different countries to providing pharmaceutical assistance to patients with orphan diseases. Data on the cost of treating patients with orphan drugs have been analysed. Approaches are summarised and recommendations are proposed to improve pharmaceutical care for patients with orphan diseases.

The results of the study are presented on 44 pages, the number of figures - 8, tables - 5, list of references - 45 titles.

Key words: orphan diseases, orphan drugs, pharmaceutical care, provision of patients.

АНОТАЦІЯ

У кваліфікаційній роботі розглянуто проблему організації фармацевтичної допомоги хворим з орфанними захворюваннями. Представлено результати аналізу даних щодо визначення статусу орфанного захворювання та їх класифікації, підходів у діагностиці та лікуванні, а також підходів у різних країнах по забезпеченню фармацевтичною допомогою хворих з орфанними захворюваннями. Проаналізовано дані щодо вартості лікування хворих орфанними препаратами. Узагальнено підходи та запропоновано рекомендації щодо покращення фармацевтичної допомоги хворим з орфанними захворюваннями.

Результати дослідження викладено на 44 сторінках, кількість рисунків - 8, таблиць - 5, список використаних джерел - 45 найменувань.

Ключові слова: орфанні захворювання, орфанні лікарські засоби, фармацевтична допомога, забезпечення пацієнтів.

CONTENT

INTRODUCTION

Actuality of topic. The provision of medications for patients with rare diseases requires substantial financial investment from the state, primarily due to the high cost of orphan drugs. This cost is driven by the significant investments needed for the development and production of these drugs, combined with low sales volumes due to the limited number of patients within the target group. Many countries have implemented government programs aimed at promoting research into both the pathogenesis of rare diseases and the development and production of medications for their diagnosis and treatment. These programs help to accelerate research and the introduction of new drugs for the treatment of orphan diseases, ensuring more effective support for patients who require specialized therapies, while also alleviating the financial burden that such diseases place on public healthcare systems.

Additionally, international organizations, such as the World Health Organization and the European Union, encourage global collaboration and knowledge-sharing among researchers, healthcare providers, and pharmaceutical companies to improve outcomes for rare disease patients. Partnerships between government entities and private pharmaceutical firms are also on the rise, as they offer potential solutions to improve access to innovative treatments and to foster advancements in drug development. This collaborative approach is crucial, given the unique challenges that orphan diseases present, including the need for specialized expertise, resources, and patient-centered care. By working together, governments and industry stakeholders are better positioned to address the healthcare needs of this vulnerable population, drive innovation in medical research, and ultimately, enhance the quality of life for individuals affected by rare diseases.

In the long term, such initiatives aim to build a sustainable framework that enables ongoing research, early diagnosis, and effective treatment options for orphan diseases, contributing to a more inclusive and responsive healthcare system that meets the needs of all patients.

The purpose of the study is to examine strategies for organizing pharmaceutical care for patients with orphan diseases.

Research objectives:

- analyse scientific information sources on orphan diseases;
- to study the prevalence of orphan diseases among the population of the world;
- examine the challenges in providing pharmaceutical care for patients with orphan diseases worldwide;
- analyze the practices of government regulation in pharmaceutical care for patients with orphan diseases;
- assess the pharmaceutical market for medications used in the treatment of orphan diseases;
- evaluate strategies for enhancing the organization of pharmaceutical care for patients with orphan diseases.

The object of study: publications and research results related to pharmaceutical care for patients with orphan diseases, morbidity and prevalence rates; regulatory legal documents. Subject of the study: theoretical, methodological, applied foundations of the organisation of pharmaceutical care for patients with orphan diseases.

Research methods. In the analysis methods of the content analysis, comparative, analytical, statistical, graphical methods were used.

Structure and scope of qualification work. The qualification work consists of the introduction, three chapters, conclusions to each chapter, general conclusion, and list of used sources. The results of the study are presented on 44 pages of text, the number of figures - 8, tables - 5, and the list of references - 45 titles.

CHAPTER 1. ORPHAN DISEASES AS A MEDICAL AND SOCIAL PROBLEM

1.1. Definition and classification of orphan diseases

Orphan (rare) diseases represent a significant medical and social problem for most countries in the world. These diseases affect a relatively small proportion of the population, but for each individual patient and his or her family, the consequences of their occurrence can be very serious. Because orphan diseases are rare, public and medical attention to them has long been insufficient, leading to difficulties in diagnosis, treatment and social support for patients. Today, thanks to the active efforts of the international medical community and states, the situation is gradually changing and rare diseases are beginning to be considered as an important object of research and social programmes [4, 7, 19].

The term "orphan diseases" was introduced in the United States in 1983 with the enactment of the Orphan Drug Act, which identified 1,600 rare diseases for which causes and treatments were largely unknown. Following this, several other countries implemented similar laws to regulate the development, production, and use of orphan drugs: Singapore in 1991, Japan in 1993, and Australia in 1997 [37, 43].

The term ‘orphan’ highlights their rarity and is related to the fact that, until recently, they have not attracted much attention from pharmaceutical companies and public health programmes. These diseases are characterised by diverse manifestations, are often genetic in nature, and are often life-threatening or significantly impair a patient's quality of life [37].

However, there is no universally accepted definition of rare diseases. In some definitions, the rarity is based solely on the number of people affected, while in others, additional factors are considered, such as the feasibility of treatment or the potential to alleviate symptoms. Medical literature reflects these variations, with

definitions specifying prevalence rates that can range from 1 in 1,000 to as rare as 1 in 200,000 [1, 4].

To date, there are more than 8,000 known orphan diseases, the vast majority of which are caused by genetic mutations. However, there are also rare infectious and autoimmune diseases that are included in the category of orphan diseases. Cystic fibrosis, Gaucher's disease, haemophilia, Huntington's disease, phenylketonuria and many others are examples of orphan diseases [1, 4].

There are several approaches to the classification of orphan diseases, but in general it is a complex process, as these diseases have a variety of causes, course and clinical manifestations. Orphan diseases can be divided into several major categories depending on various factors such as genetic nature, age of onset, severity of course, prognosis, and the fields of medicine that study and treat them [2-5, 19, 38, 42]. The most common approaches to categorising orphan diseases are presented below (tabl. 1.1).

Table 1.1

The classification of orphan diseases

Classification Feature		Characterisation
by disease severity and prognosis	life-threatening diseases	diseases that, without treatment or with ineffective treatment, result in the death of the patient (e.g. spinal muscular atrophy, Gaucher disease, severe forms of mucopolysaccharidosis)
	chronic and debilitating diseases	diseases often present with chronic symptoms that impair the patient's quality of life, but are not necessarily directly life-threatening (e.g., rare forms of epilepsy, neurofibromatosis and Behçet's disease)
by origin and etiology	genetic diseases	diseases caused by genetic mutations or inherited defects (cystic fibrosis, Down syndrome, phenylketonuria, Tay-Sachs disease, Duchenne muscular dystrophy and others). They account for about 80% of all orphan diseases.
	non-genetic diseases	diseases can be caused by infections, autoimmune processes, environmental influences or other factors (rare forms of cancer, infectious diseases (like

		leprosy), and autoimmune diseases (like systemic lupus erythematosus))
by age of onset	diseases manifesting in childhood	orphan diseases manifest from birth or early childhood (spinal muscular atrophy, phenylketonuria, and congenital adrenal hyperplasia)
	diseases manifesting in adulthood	orphan diseases do not begin to manifest until adulthood, making early diagnosis difficult (Gaucher disease, Fabry disease and Marfan syndrome)
by organ or systemic localisation	neurological diseases	diseases affecting the nervous system (Rett syndrome, amyotrophic lateral sclerosis, Batten disease)
	metabolic diseases	Metabolic diseases like phenylketonuria, Fabry disease, Pompe disease, Hunter syndrome
	cardiological diseases	Rare cardiovascular diseases like arrhythmogenic right ventricular dysplasia, Brugada syndrome
	dermatological diseases	Rare skin diseases such as ichthyosis, bullous epidermolysis
	respiratory diseases	diseases affecting the respiratory system, such as cystic fibrosis and idiopathic pulmonary fibrosis
by type of inheritance (for genetic diseases)	autosomal dominant diseases	diseases in which a single altered gene from one of the parents is sufficient for their manifestation (Marfan syndrome)
	autosomal recessive diseases	Diseases that manifest only if the mutated gene is present in both copies, derived from both parents (cystic fibrosis and phenylketonuria)
	sex-linked (X-linked) diseases	Diseases in which the mutated gene is on the sex X chromosome; these diseases often occur in males because they have only one X chromosome (haemophilia and Lesch-Nyhan syndrome)
	mitochondrial diseases	diseases caused by mutations in mitochondrial DNA; since mitochondrial DNA is inherited exclusively from the mother, such diseases are passed down the maternal line (Ley syndrome and myoclonus epilepsy with vomiting)

by prevalence	very rare diseases	diseases that occur in 1 in 100,000 or less. These are the rarest and least studied diseases, for which there are often not even statistics or treatments available
	rare diseases	diseases that occur in 1 in 10,000 to 1 in 100,000 people. This includes many types of orphan diseases that may be rare enough to cause significant problems with access to diagnosis and treatment
by clinical progression	progressive diseases	diseases tend to worsen the patient's condition over time (amyotrophic lateral sclerosis or Huntington's disease)
	remitting diseases	diseases that can go through stages of remission and exacerbation; these diseases often make it difficult to predict how and when the condition will worsen (lupus and some rare autoimmune diseases)
by treatability	treatable diseases	Orphan diseases for which there are effective treatments that can control symptoms and prevent disease progression (phenylketonuria (with diet) and Gaucher disease (with enzyme replacement therapy))
	difficult to treat or incurable diseases	Diseases for which there are no effective treatments and medical care is limited to supportive measures (amyotrophic lateral sclerosis and some forms of mucopolysaccharidosis).
by availability of drug therapy (orphan drugs)	diseases with registered orphan drugs	These diseases include those for which specific drugs, called orphan drugs, have been developed and are available. For example, cystic fibrosis and Gaucher disease
	diseases without registered orphan drugs	Some rare diseases still have no registered drugs, making them difficult to treat and requiring the development of new drugs.

It can be argued that the classification of orphan diseases allows for a better understanding of their nature and the most effective approaches to their diagnosis, treatment and prevention. Such structured information also helps in the development of government programmes and policies to support rare disease patients to improve their quality of life and access to medical and pharmaceutical care.

1.2. Study of the prevalence of orphan diseases in the world

According to current standards, a disease is classified as an orphan disease if it affects no more than 1 in 2,000 people or is one of 500 rare diseases affecting fewer than 1 in 1 million people [1, 4]. Definitions can also vary by region; for instance, in the Canadian province of Alberta, a condition is considered rare if it occurs in 1 in 50,000 individuals, whereas in Ontario, it is defined as affecting 1 in 100,000 to 150,000 people. In the United Kingdom, additional classifications have been introduced, such as ‘ultra-rare DRs’ and ‘ultra-rare diseases,’ which encompass conditions affecting fewer than 1,000 individuals across the entire country [32, 37, 42-43].

The prevalence of diseases of this group (according to the documents of the European Society) is presented in fig. 1.1.

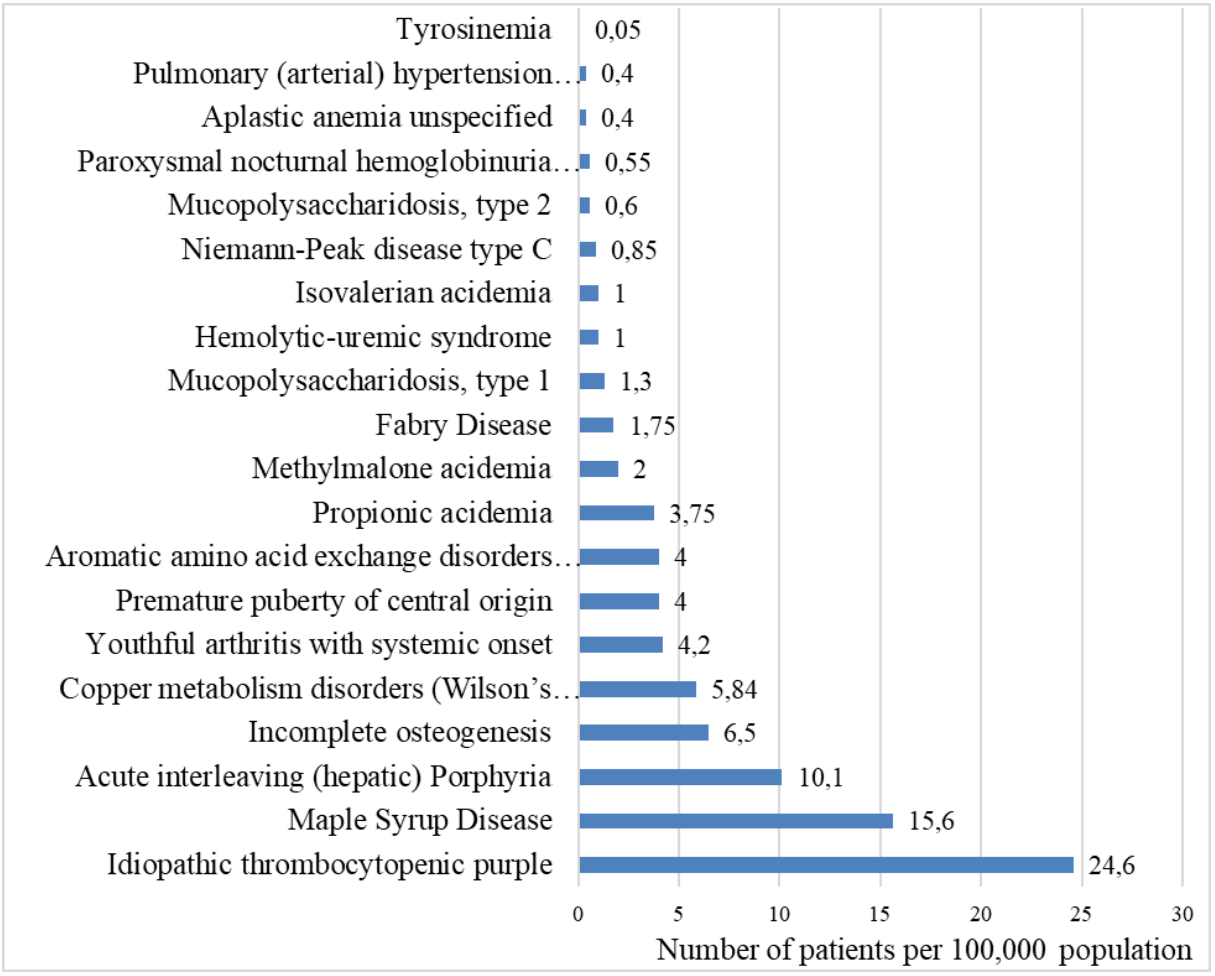

Fig. 1.1. Prevalence of diagnosis of individual nosological forms of orphan diseases

It should be noted that the collection of statistical data on the prevalence of orphan diseases in countries around the world has a number of specific features and difficulties due to the rarity of these diseases, differences in the criteria for their definition, and poorly developed tracking systems. Thus, several limitations in creating a unified approach can be seen.

Firstly, there are differences in the criteria for defining orphan diseases. As mentioned above, different countries use their own criteria for determining the rarity of a disease. For example, in the European Union, a disease is considered an orphan if it occurs in less than 1 in 2,000 people, whereas in the United States the rate is 1 in 200,000 people. These differences make it difficult to compare data between countries and regions. In addition, some countries have introduced the concept of 'ultra-rare' diseases, making it difficult to harmonise criteria and classifications for international analysis [1, 7, 19, 28].

Secondly, there is the problem of limited diagnostic facilities and lack of awareness among doctors. First of all, many orphan diseases are not diagnosed at early stages due to lack of awareness among medical professionals and lack of specialised diagnostic tests. As a result, many cases go unrecorded and prevalence data are underestimated [32]. Also, the diagnosis of some orphan diseases requires expensive and sophisticated equipment that is not available in all health facilities, especially in low-income countries. The financial and resource constraints of each country can also be a barrier to the collection of statistical information. In countries with limited resources, this may result in a lack of quality information on the prevalence of orphan diseases. Even in countries with more developed health systems, the lack of prioritisation of orphan diseases limits their reporting and monitoring [11].

Third, many countries do not have national registries of orphan diseases that systematically collect information on diagnoses, prevalence, treatment and mortality. Such registries, if they do exist, have varying levels of detail and are often not standardised. In addition, there is a lack of centralised data on patients with

orphan diseases, making it difficult to obtain accurate statistics and impossible to estimate global prevalence [4, 5].

Fifth, there is currently a problem with disease coding, as due to the rarity of these diseases, they may not be adequately covered by existing coding systems (e.g. in the International Classification of Diseases - ICD). As a result, some diseases do not receive unique codes, making them difficult to register and statistically record. In addition, even when codes for some diseases are available, it may be difficult for physicians to use them correctly due to a lack of experience in diagnosing orphan diseases [1, 10, 19].

There is also a psychological and social problem. For example, due to the rarity and severity of orphan diseases, patients and their families may experience social and psychological difficulties, which may lead them not to seek medical help and thus not be included in official statistics. In turn, the stigmatisation of rare diseases may also lead to patients avoiding diagnosis and treatment [16, 43].

Also it is precisely because of under-reporting and under-recording of cases that orphan diseases often remain underestimated in statistics, which may be related to both under-detection due to the difficulty of diagnosis and low awareness among doctors and patients [36].

There is also a lack of international coordination in the collection and analysis of epidemiological indicators for orphan diseases. Although there are organisations, such as EURORDIS, that are working to improve conditions for patients with orphan diseases and to collect data, there is no single global database to track the prevalence and treatment of orphan diseases worldwide [5, 10]. This makes international co-operation and data sharing difficult. It is precisely this sharing that could be the pathway to solving the problem of diagnostics and drug supply for patients with orphan diseases.

As a rule, orphan diseases significantly reduce the quality and length of life. The life expectancy of patients varies widely among nosologies. For example, some degenerative and life-threatening diseases lead to death almost immediately after

birth, while others are compatible with a normal life if diagnosed in time and treated properly, such as phenylketonuria [6, 11, 27].

Based on the analysis of scientific literature, we have developed a general characterisation of orphan diseases (fig. 1.2).

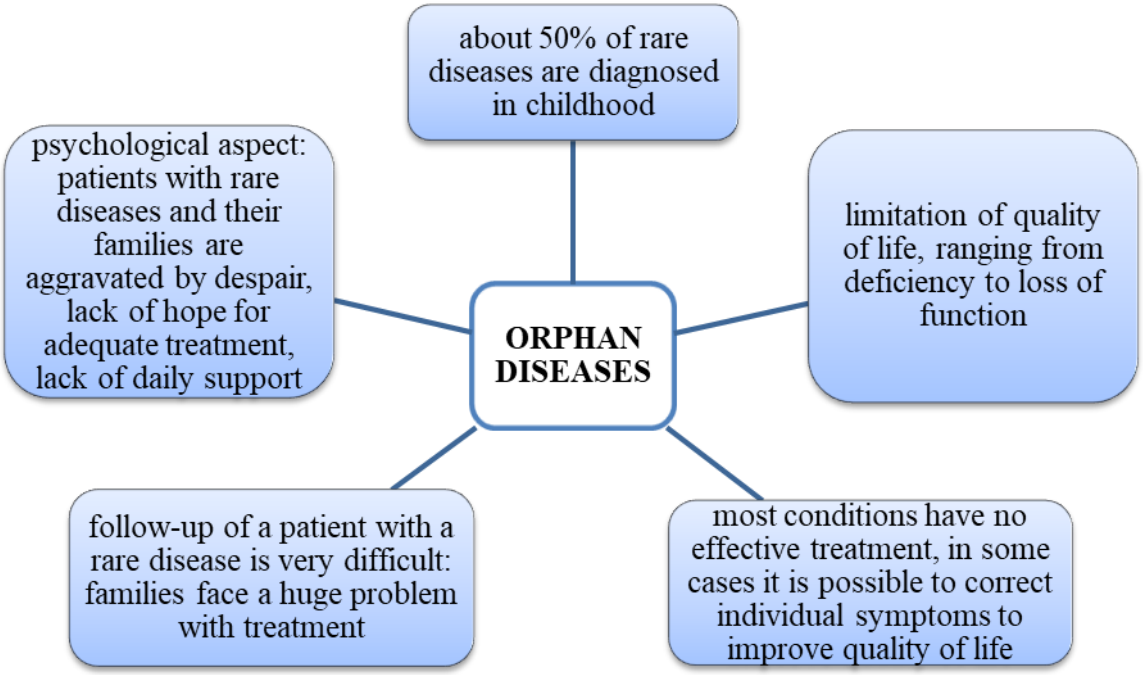

Fig. 1.2. General characterisation of orphan diseases

1.3. Social aspects and significance of the problem of orphan diseases

Orphan diseases are not only a medical problem, but also a serious social problem. Patients suffering from rare diseases often experience significant difficulties in everyday life and need constant medical and social support. In some cases, such diseases lead to disability, which limits the patients' ability to work and social integration.

Patients with rare diseases face physical, psychological, and logistical challenges in their everyday lives. Many rare diseases, such as muscular dystrophy, cystic fibrosis, and certain metabolic disorders, impose limitations on patients' mobility, strength, and endurance. As a result, simple tasks, such as walking, eating,

and performing personal hygiene, may become difficult, requiring assistance from caregivers or specialized equipment [38, 43].

For instance, individuals with cystic fibrosis require regular physiotherapy and special breathing exercises to manage their condition. Additionally, they must adhere to a strict regimen of medications and treatments to manage their symptoms. This not only affects their physical health but also places emotional and social stress on them and their families. The constant medical attention required can lead to social isolation, as it is difficult for them to participate fully in normal daily activities or socialize with peers [43].

Due to the chronic nature of many orphan diseases, patients often rely heavily on family members for support. Parents of children with rare diseases, such as Rett syndrome or spinal muscular atrophy, often become full-time caregivers, which can limit their employment opportunities and place a financial burden on the family.

In many cases, family members must adjust their lives significantly, sometimes even quitting their jobs to provide constant care. This dependency can cause significant stress within the family, leading to emotional, psychological, and financial strain. Families with limited financial resources may struggle to afford specialized care, assistive devices, and ongoing treatments, especially in countries without strong social welfare systems [2-4, 43].

Patients with orphan diseases often require ongoing medical and social support due to the limitations caused by their condition. For example, the mucopolysaccharidosis disease affects the musculoskeletal system, vision and hearing. Patients, especially children, require constant physiotherapy, orthopaedic care and specialised medical equipment [9,11, 33].

According to the European Organisation for Rare Diseases (EURORDIS), about 85% of patients with orphan diseases have chronic conditions that require lifelong treatment and care. This results in an inability to perform simple activities independently, such as travelling, cooking or attending work/study. Patients become dependent on relatives or social services [11, 33, 35] .

In addition, studies have shown that the high cost of treatment makes orphan diseases a serious social problem. For example, treatment of one patient with Gaucher disease (using enzyme replacement therapy) can cost 250-400 thousand US dollars per year. Overall, in the USA, according to the National Organisation for Rare Diseases (NORD), the total cost of treating orphan diseases reaches $20 billion annually [37-42]. Another example is the treatment of spinal muscular atrophy with Zolgensma, which can cost up to $2.1 million per dose, making it one of the most expensive drugs in the world [38, 41].

Many patients with orphan diseases and their families face emotional, financial and social difficulties that are associated with the need for long-term treatment and specialised care. Drugs for rare diseases, so-called ‘orphan drugs’, are often very expensive due to limited production and unique development technologies. In some countries, patients have to pay for them themselves, which creates additional difficulties for families. In countries with less developed healthcare systems, patients' families are forced to find funds for treatment on their own, resulting in debt, the sale of property and a significantly reduced quality of life [37, 38, 41].

In addition, patients with orphan diseases often suffer from isolation and stigmatisation, especially when the disease causes physical changes or severe symptoms. Society in general is poorly informed about these diseases, leading to misunderstanding and lack of support for these patients. For example, children with epidermolysis bullosa (so-called ‘butterfly children’) have skin that is so fragile that it can be damaged by even the slightest touch. This makes it impossible for them to participate in normal school activities [32, 36].

According to EURORDIS research, 30 % of children with orphan diseases in Europe either do not attend school at all or are educated at home, which limits their social development and career prospects in the future [38, 41].

Patients with Ehlers-Danlos syndrome face mistrust from others because their symptoms (e.g. chronic pain or joint dislocations) often have no visible manifestations. This causes difficulties in obtaining disability or social assistance [38].

According to the NORD study, 95 % of patients with rare diseases feel isolated and 65 per cent of families face a lack of available support resources [42].

Conclusions to chapter 1

Orphan diseases are an urgent problem of modern healthcare and society as a whole. Awareness of this problem is the first step to help patients with rare diseases and their families, as well as to prevent rare pathology.

It is determined that there are many approaches to the classification of orphan diseases, taking into account their etiology, severity of course, occurrence in different age groups of patients, localisation, genetic predisposition, prevalence, clinical progress, and possibility of treatment.

It is revealed that in many countries orphan (rare) diseases are recognised as an independent class of diseases, the criterion of prevalence of these diseases is established.

There are various types, approaches and methods of prevention of rare diseases. Medical and genetic counselling with prenatal diagnosis aimed at preventing the birth of a child with a non-orrigible disease are effective.

It has been determined that orphan diseases require special attention not only from the medical community, but also from society as a whole. Patients face many difficulties, ranging from the high cost of treatment to social isolation. Addressing these problems requires a systematic approach, including the development of government programmes, support for scientific research and ensuring inclusiveness for patients with rare diseases.

CHAPTER 2. ANALYSING APPROACHES TO REGULATING THE PROVISION OF DRUGS TO PATIENTS WITH ORPHAN DISEASES

2.1. Analysing the principles of pharmaceutical support for patients with orphan diseases in the world

Each rare disease is unique and demands a tailored, individualised approach to treatment. Consequently, the medications designed for rare diseases are also highly specialised. These drugs are only required by a small group of patients with specific rare conditions and are therefore produced in very limited quantities by a small number of manufacturers [5, 16].

Orphan drugs are pharmaceutical products developed for the diagnosis, prevention, or treatment of rare diseases or conditions that pose significant risks to a patient’s health or life. They are referred to as "orphan" drugs because, in a market-driven economy, the pharmaceutical industry often lacks financial incentives to develop and distribute medications intended for such a small patient population [12, 16].

This is primarily because the anticipated revenue from the sale of these medicines is insufficient to offset the exceptionally high expenses pharmaceutical companies incur in their development and launch. Moreover, since the market for treatments involving such drugs is relatively small, the manufacturers face significant financial losses [1, 23].

As a result, these medications are often prohibitively expensive, which is why European countries strive to ensure patients with rare diseases have the widest possible access to these treatments through public funding. A major challenge remains the treatment itself, largely due to its high cost [26].

Currently, several countries, including the European Union, the United States, Japan, Taiwan, Singapore, and Australia, have implemented specific legislation aimed at incentivising scientific research and encouraging pharmaceutical companies to develop drugs for the treatment of rare diseases. For instance, the

United States passed the Orphan Drug Act in 1983, which provided financial incentives, such as tax credits for clinical trials, fee waivers, and market exclusivity for seven years, to promote the development of orphan drugs. Similarly, the European Union adopted its Orphan Medicinal Products Regulation in 2000, offering ten years of market exclusivity, reduced fees, and access to special funding programs for orphan drug development [8, 27, 30, 31, 39].

The introduction of these legislative measures has facilitated significant advancements in treating rare diseases, largely due to the application of cutting-edge biotechnology. Biotechnological innovations, such as gene therapy, monoclonal antibodies, and RNA-based treatments, have made it possible to develop effective therapies for conditions that were once considered untreatable. For example, gene therapy has shown promising results in treating rare genetic disorders such as spinal muscular atrophy (SMA) and certain types of inherited blindness [10, 44].

By 2020, the U.S. Food and Drug Administration (FDA) had approved over 770 orphan drugs, while the European Medicines Agency (EMA) had authorised more than 200. Despite these advances, however, access to these treatments remains a significant challenge due to their high cost and limited availability. Nevertheless, ongoing biotechnological progress and supportive legislative frameworks continue to provide hope for patients suffering from rare and previously incurable diseases [12, 23, 27, 32].

Currently, the lack of a unified approach to the definition of orphan diseases and strategies for financial support of drug therapy contribute to the diversity of medical and pharmaceutical care for patients with orphan diseases. In many countries, the so-called ‘life-saving rule’ is in force; in the absence of alternative available treatment, patients should receive treatment regardless of its cost; insurance and reimbursement mechanisms for the purchase of drugs by patients with orphan diseases are often used [25-26].

In some countries, the reimbursement amounts from 65% (France, Finland) to 100% (Denmark, Spain, Poland) depending on the diagnosis and conditions of provision, usually the patient's stay in a medical organisation. In Japan,

reimbursement is 100%, with 30% reimbursed by insurance companies and the remaining amount repaid from local budgets [1, 5, 6].

In many states, based on the insurance principle of medicine, the federal government is responsible for ensuring the effectiveness, safety and production of orphan drugs, while the provinces (subjects) are left in charge of financial provision of reimbursement for the purchase of orphan drugs. This leads to the formation of various forms and varieties of state reimbursement depending on the economic well-being of the country, as well as to a multitude of legislative initiatives regarding the organisation of drug provision, the missing financial resources are covered by the budget of the states.

We have analysed international practice in the implementation of drug coverage strategies for patients with orphan diseases (tabl.2.1).

In the United States, manufacturers of orphan drugs are provided with tax benefits to incentivize the development of treatments for rare diseases. Moreover, special regulatory conditions are in place in the United States, Japan, and the European Union to facilitate market access for orphan drugs based on their specific medical indications. These conditions include a period of market exclusivity during which no other drug with the same indications can be registered: ten years in EU countries, seven years in the United States, and five years in Japan [1, 9].

European Union countries offer additional support to orphan drug manufacturers. This includes free assistance in drafting clinical trial protocols, a 50% reduction in customs duties at the pre-registration stage, and another 50% reduction within the first year following the drug's approval. Furthermore, an accelerated document review process during registration is available, along with the possibility of obtaining approval based on incomplete clinical trials. Certain countries, such as Italy and Spain, also regulate the trade margin for orphan drugs, capping it at a maximum of EUR 7.5 per package [1, 6].

Table 2.1

Comparative characterisation of regulatory strategies for orphan drugs

Country	Prevalence rate for the definition of an orphan disease	Availability of the state programme	Legislative acts / authorities, organisations, programmes	Key points
U.S.A.	1 case per 20,000 population	+	The Orphan Drugs Act (1983)	It is proposed to amend the relevant federal laws to reduce the cost of developing these drugs and provide financial incentives to pharmaceutical companies in the development of these drugs. Recommendations for research on rare medicines and the terms of their licensing are established. The terms of patent protection of the drug and its validity period are provided for. The guarantors and terms of the manufacturer's contract with organisations for the production of drugs for the treatment of rare diseases are defined. The procedure for quality control of these drugs is established.
			The Rare Disease Act (2002)	Established the Office of Rare Diseases. Federal funding for the development of treatments for rare diseases is increased
			National Institute for Medical Research Programmes	Conducting research into rare diseases and focusing on diagnosis
Canada	Less than 5 cases per 10,000 population	+	Health Canada's Special Access Programme	providing access to several orphan drugs for patients with rare diseases
			Orphan Drug Structure The Canadian Organisation for Rare Diseases (CORD)	5 strategic goals: Detection and prevention, Timely, Equitable and evidence-based care, Support for the patient community, Access to promising treatments and research.

Bulgaria	Less than 5 cases per 10,000 population	+	The National Plan (2009-2013)	ensuring prevention, diagnosis, treatment and rehabilitation of patients with rare diseases
France	Less than 5 cases per 10,000 population	+	The first national plan (2005-2008)	Improve knowledge of the epidemiology of rare diseases, recognise the characteristics of rare diseases, develop information on rare diseases for patients, medical professionals and general public health professionals, organise access to diagnostic tests, continue efforts in favour of orphan drugs, comply with the requirements of social services for patients with rare diseases, and develop national and European partnerships
			The Second National Plan (2011-2014)	improving the quality of care for patients through the use of reference centres and telemedicine, developing research on rare diseases such as translational clinics and therapeutic research, and expanding European and global cooperation.
Germany	Less than 5 cases per 10,000 population	+	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE)	include care/ centres/ networks, research, diagnostics, information management, patient orientation, registries, and implementation and future development
UK	Less than 5 cases per 10,000 population	+	UK Rare Disease Strategy	examines patients and their families. Includes empowerment of patients with rare diseases, detection and prevention of these diseases (screening and carrier testing), diagnosis and early intervention, coordination of care (specialised centres) and research. The strategy ensures work with other countries affected by rare diseases as well.
Australia	1 case per 10,000 people	–	Orphan Drug Policy (1998)	The conditions for obtaining patent protection for orphan drugs are established. The conditions for accelerated consideration of documents during the registration of these drugs are provided.
Japan	4 cases per 10,000 people.	+	Orphan Drug Regulation (1993)	It provides for patent protection for orphan drugs for a period of 10 years. Tax benefits for companies producing orphan drugs are stipulated. The conditions for accelerated review of documents during registration are established.

Germany has implemented a network of specialized centers dedicated to the treatment of patients with rare diseases. These centers operate under the ‘compassionate use’ program, which allows the experimental use of drugs that have not yet received official approval. This approach not only provides critical treatment options for patients but also facilitates clinical trials of orphan drugs, enabling their faster development and evaluation [6].

Despite these initiatives, the primary responsibility for supporting patients with orphan diseases still rests on the state. Governments continue to bear the significant financial burden of ensuring access to these high-cost therapies and providing the necessary care for affected individuals [6].

Research shows that over the past decades, the global community has made significant progress in improving the provision of medicines for patients with orphan diseases. Thanks to the adoption of special legislative initiatives, such as the Orphan Drug Act in the USA, similar programmes in Europe, Japan and other countries, there has been an increase in the availability of medicines for the treatment of rare diseases.

At the state level, countries are introducing comprehensive approaches to improve diagnosis, treatment and provision of patients with orphan drugs. For example, EU countries have created a system of incentives for pharmaceutical companies, including tax benefits, accelerated registration procedures and exclusive rights to sell drugs for up to 10 years. In Germany, there is a network of specialised centres for the treatment of patients with rare diseases, which makes it possible to effectively conduct both treatment and clinical trials of new drugs. In the US, government programmes have helped more than 600 drugs for orphan diseases to receive FDA approval, which has significantly improved the quality of life for millions of patients.

At the global level, the introduction of new biotechnologies makes it possible to develop innovative drugs capable of treating previously untreatable rare diseases. For example, gene therapy has become a real breakthrough in the treatment of rare genetic diseases such as spinal muscular atrophy. Joint efforts by countries to

establish international patient registries and share data are significantly improving diagnosis and treatment standards. However, the problem remains, firstly, the proper regulation of all the processes of providing this category of patients, and secondly, financing.

Therefore, the next step was to analyse the regulatory framework for the circulation of orphan drugs in countries around the world.

2.2. Legal framework for the regulation of orphan drugs around the world

To classify a drug as an orphan drug, the applicant—at any stage of the drug's development prior to obtaining a marketing license—must submit a formal application to the Committee for Orphan Medicinal Product Recognition and Tracking (COMP). This application must contain detailed and specific information about the drug and its intended purpose. The key elements required in the application are as follows (fig. 2.1).

The process of reviewing these applications involves a thorough assessment by regulatory authorities to ensure that the proposed drug meets the criteria for orphan designation. If approved, the drug may qualify for specific incentives, such as tax credits, fee waivers, grants for clinical research, and market exclusivity, which encourage the continued development of treatments for rare diseases. This regulatory framework plays a vital role in addressing the unique challenges posed by orphan diseases and ensures that patients with these conditions have access to effective therapies.

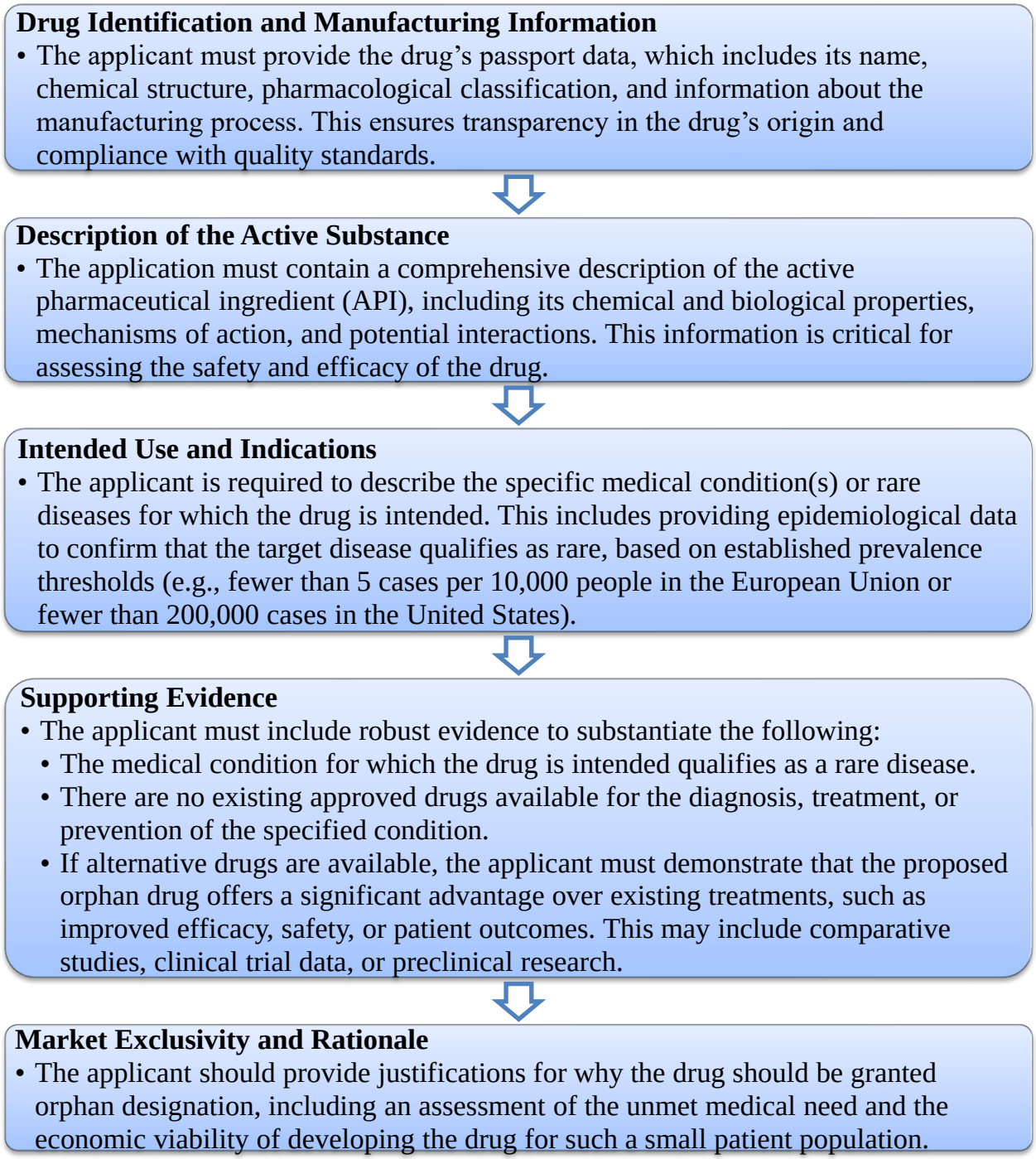

Fig. 2.1 The main elements of an application to recognise a drug as an orphan

If the information in the submitted materials is insufficient to make a decision, the COMP may request additional information. When preparing the conclusion, if consensus is not reached, the decision is made based on the opinion of the majority (at least 2/3 of the total number of EMA members). The period for reviewing the sponsor's application is 90 days. If a negative decision is made, the applicant may file an appeal within 90 days, to which the EMA must respond within 30 days. If the

EMA decides positively, the drug will be approved as an orphan drug for the rare disease for the indication specified in the orphan drug application. For other indications, the sponsor must submit another orphan drug application for a "new" indication [1, 5].

The results of the analysis of regulatory documents [8, 21, 22, 27, 30-32], the provisions of which determine the procedure for determining the status of an orphan drug, the requirements for it, are presented in table 2.2.

Table 2.2

Key regulatory documents governing the approval and licensing of orphan drugs

Document	Requirements
Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products	• establishes the basic requirements for orphan drugs • defines the main types and forms of stimulation of development and production of orphan drugs. • regulates the rights and obligations of the Committee on Orphan Drugs (COMP)
Commission Regulation (EC) No 847/2000 of 27 April 2000	• Clarified key definitions • Presented key requirements for orphan drug marketing
Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products	Communication from the European Commission setting out: • the procedure for approval of orphan drugs • provisions on market exclusivity for orphan drugs
Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004	The issues of centralization of the procedure for approval of orphan drugs in the EU are reflected
Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use	The requirements for granting conditional marketing authorisation for medicinal products falling within the scope of Regulation (EC) No 726/2004 are described.
Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006	Regulates issues of exclusivity of orphan drugs (if the drug is being developed for treatment in the pediatric population, the

on medicinal products for paediatric use	exclusivity period can be extended to 12 years)
Commission Regulation (EC) No 2049/2005 of 15 December 2005	Regulates the provision of preferences to small businesses - manufacturers of orphan drugs
Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity	The main principles of demonstrating “similarity of medicinal products” and clarifications on issues of exclusivity of orphan drugs are presented
Standard operating procedure SOP/H/3190. Review of orphan designation at the time of granting/varying a marketing authorisation	Standard Operating Procedure (SOP) that sets out in detail the process for licensing an orphan drug (or making changes)
Standard operating procedure for orphan medicinal product designation and maintenance SOP/H/3534	SOP, which details the procedure for approving an orphan drug
Checking-in and electronic filing of documentation for orphan medicinal product designation. SOP/H/3047	SOP that details the electronic submission of an application for approval of an orphan drug
EMA/COMP/15893/2009 Final: Recommendation on Elements Required to Support the Medical Plausibility and the Assumption of Significant Benefit for an Orphan Designation	Guidelines for demonstrating the lack of treatments for a rare disease (demonstrating "medical plausibility")
Procedural advice for orphan medicinal product designation: Guidance for sponsors EMA/420706/2018	Guidelines for sponsors, which detail the application and EMA review procedures

Although the EMA provides a unified framework, individual European countries may have additional support mechanisms, such as specialized funding programs, tax incentives, or reimbursement policies for orphan drugs. For example, Germany established a network of specialized centers for treating rare diseases and allows for the "compassionate use" of unapproved drugs for patients with critical needs. France has specific programs to expedite access to orphan drugs before marketing authorization through its Temporary Authorization for Use (ATU) scheme. Italy and Spain implement limits on trade margins for orphan drugs to ensure their affordability [1, 5, 11, 18, 21, 32].

Despite the comprehensive regulatory framework, challenges remain, such as disparities in access to orphan drugs across EU member states due to differences in healthcare funding and reimbursement systems. Additionally, the high cost of orphan drugs often poses a burden on public healthcare systems, necessitating ongoing adjustments in policies to balance innovation and affordability.

Thus, the determination of orphan drug status in Europe is a well-structured process that aims to encourage the development of treatments for rare diseases while ensuring that such therapies address unmet medical needs and are accessible to patients

Conclusions to chapter 2

The United States was the first country to introduce a national support system for the development of orphan drugs, underpinned by robust legislation. This system represents the most advanced legal framework globally for regulating the development, circulation, and use of medications specifically intended for the treatment of rare diseases. The establishment of such a system laid the foundation for other nations to follow suit in addressing the challenges associated with rare disease treatment.

Countries adopted several supportive measures to promote the research, development, and production of orphan drugs. These include an accelerated drug

registration process, significant tax benefits for pharmaceutical companies, and the granting of exclusive marketing rights for newly developed treatments. These measures not only incentivize pharmaceutical manufacturers to invest in treatments for rare conditions, which often lack profitability, but also drive innovation and contribute to expanding the range of orphan drugs available to patients. As a result, the list of approved orphan drugs continues to grow, providing new hope for patients suffering from rare and previously untreatable diseases.

CHAPTER 3. ANALYSIS OF PHARMACEUTICAL CARE SYSTEMS FOR PATIENTS WITH ORPHAN DISEASES

3.1 Analysis of the current state of the orphan drugs market

The pharmaceutical market for orphan drugs has grown significantly in recent years due to advancements in medical research and supportive legislative frameworks in various countries. Orphan drugs are designed to treat rare diseases, which affect a small percentage of the population but often have life-threatening or debilitating consequences. Despite their high development costs and limited patient base, incentives such as tax benefits, market exclusivity, and fast-track approvals have encouraged pharmaceutical companies to invest in this field [17, 39].

The orphan drug market is a growing and highly specialized segment of the pharmaceutical industry, driven by the need to address rare and often life-threatening diseases. These drugs are specifically developed to treat conditions affecting small patient populations, typically fewer than 200,000 people in the U.S. or fewer than 1 in 2,000 in the EU. Despite their niche focus, the orphan drug market has seen significant expansion, with its value projected to exceed 300 billion USD globally by 2030 [17, 38, 44]. However, the market is characterized by high drug costs, presenting affordability and accessibility challenges for healthcare systems worldwide.

In 2022, the global orphan drugs market was valued at 157 billion USD and is expected to grow significantly, reaching approximately 484.73 billion USD by 2032. This expansion reflects a remarkable compound annual growth rate (CAGR) of 12.2% over the forecast period from 2023 to 2032 [24].

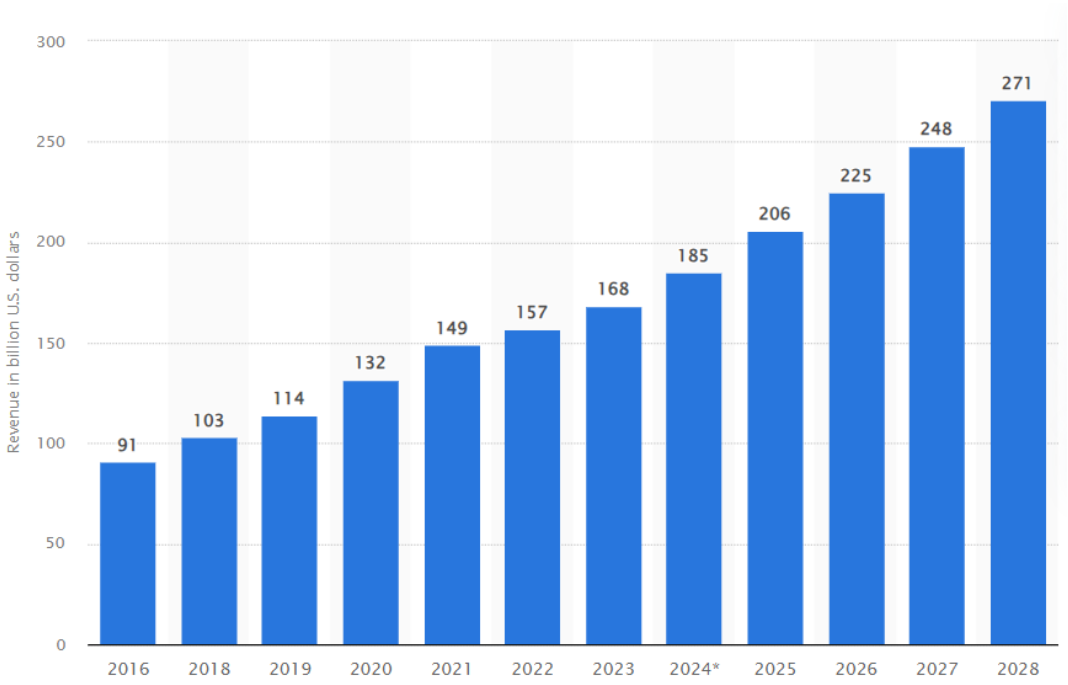

Fig. 3.1 Global sales of prescription orphan drugs from 2016 to 2028 (*forecast 2024-2028)

The oncology segment holds the largest share of the global orphan drugs market and is expected to grow at a higher CAGR during the forecast period. This growth is driven by an increasing number of clinical advancements in oncology and the availability of orphan drug treatments for cancer patients. For example, in June 2022, ALX Oncology Holdings Inc. received orphan drug designation (ODD) from the U.S. FDA for Evorpacept, a treatment for patients with Acute Myeloid Leukaemia. Additionally, significant investment in oncology by investors seeking to develop rare treatments for patients with rare cancer disorders further propels the dominance of this segment in the orphan drugs market [21, 44].

The haematology segment is anticipated to become the second-largest segment due to the growing number of approvals for haematological orphan products and the rising prevalence of rare haematological diseases among the population [21, 44].

The neurology segment is also expected to experience significant growth over the forecast period, driven by increasing incidences of rare neurological conditions such as Duchenne muscular dystrophy, multiple sclerosis, and neurometabolic

disorders [21, 44].

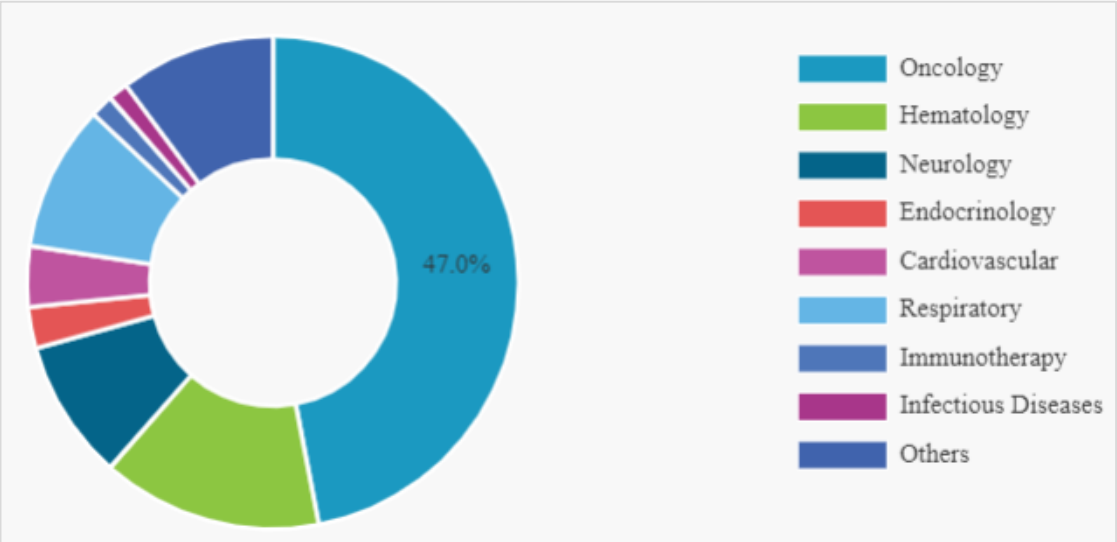

Fig. 3.2 Global orphan drugs market share (by therapy area, 2022)

In 2023, the orphan drugs market size in North America was valued at USD 91.97 billion, maintaining its dominance due to substantial expenditure on orphan drugs, a robust patient population, and the presence of leading market players driving the development of advanced and innovative treatments. The region also benefits from favorable reimbursement policies and a strong focus on addressing rare diseases [17, 21].

According to the Genetic and Rare Diseases (GARD) Information Center, over 10,000 rare diseases affect approximately 1 in 10 people, or 30 million individuals, in the U.S. This extensive patient population underscores the demand for orphan drugs in the region. For example, in December 2023, BioVersys AG received orphan drug designation (ODD) from the U.S. Food and Drug Administration for alpibectir (BVL-GSK098) and an ethionamide fixed-dose combination for the treatment of tuberculosis [7, 21, 44].

The European market is expected to exhibit steady growth due to an expanding patient base and the increasing adoption of advanced rare disease therapies. Favorable government initiatives and policies supporting research and development further boost the region’s growth prospects [7, 44].

Asia Pacific is projected to witness the highest growth rate during the forecast

period, driven by rising healthcare expenditure, improved awareness of rare diseases, and expanding healthcare infrastructure. Meanwhile, markets in Latin America and the Middle East & Africa are anticipated to grow at a slower pace due to limited access to orphan drugs and underdeveloped healthcare systems. However, these regions present opportunities for future market expansion as awareness and access improve over time [21, 44].

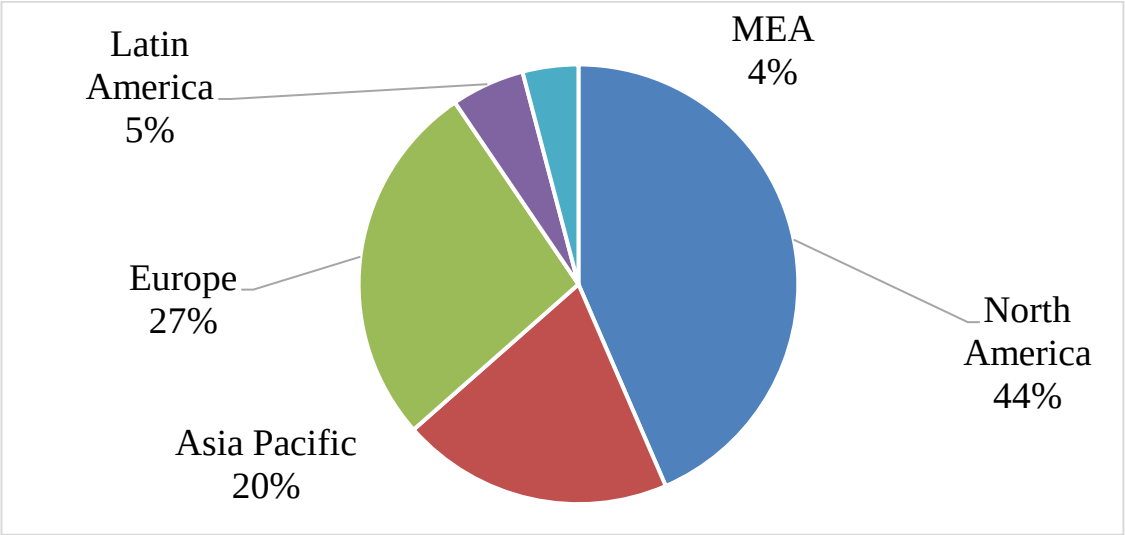

Fig. 3.3 Orphan drugs market share (by region, 2022)

According to the analytical company Emergen Research, the TOP-10 companies in terms of sales of orphan drugs for four years have been Pfizer Inc., AbbVie Inc., Novartis AG, Amryt Pharma plc, Amgen Inc., GSK plc., JOHNSON & JOHNSON, Sanofi, Hoffmann-La Roche Ltd, Takeda Pharmaceutical Company Limited. The leader in this indicator is Hoffmann-La Roche Ltd with sales of orphan drugs on the world market from $71.88 billion in 2022 (table 3.1) [24].

Table 3.1

Top 10 Globally leading companies in the orphan drug market in 2022

Place in Top 10	Company name	Annual Revenue, USD Billion	Characteristic
1	Hoffmann-La Roche Ltd	71.88	Roche, driven by a commitment to innovation, has achieved remarkable advancements in the treatment of rare diseases with groundbreaking drugs such as Hemlibra and Ocrevus, solidifying its

			prominent presence in the orphan drug market.
2	Pfizer Inc.	61.50	In recent years, Pfizer has established itself as a leader in the orphan drug market, developing innovative treatments for rare diseases, including hemophilia and Duchenne muscular dystrophy.
3	Sanofi	50.26	Sanofi Genzyme remains at the forefront of rare disease treatment, offering therapies for conditions such as Gaucher and Fabry disease. Backed by orphan drug designations and comprehensive patient support programs, Sanofi reinforces its dedication to addressing unmet medical needs and enhancing patient outcomes.
4	GSK plc.	38.61	In recent years, GSK has prioritized expanding its footprint in the orphan drug market, striving to meet the unmet medical needs of patients with rare diseases.
5	JOHNSON & JOHNSON	28.38	The company has achieved notable progress in the orphan drug market by developing treatments for rare conditions like Erdheim-Chester disease and several types of cancer.
6	Takeda Pharmaceutical Company Limited	27.79	Takeda holds a prominent position in the orphan drug market, pioneering advanced therapies for rare conditions like hereditary angioedema and Hunter syndrome.
7	AbbVie Inc.	12.31	AbbVie has achieved notable advancements in the orphan drug market, particularly through the development of innovative treatments such as Orilissa for endometriosis and Skyrizi for psoriasis.
8	Novartis AG	12.12	Novartis has achieved remarkable progress with groundbreaking treatments like Exjade, designed to address iron overload, and Afinitor, developed for specific types of tumors.
9	Amgen Inc.	7.44	Focusing on biologic therapies, the company has introduced groundbreaking treatments for rare diseases, including Prolia for osteoporosis and Blincyto for acute lymphoblastic leukemia. Amgen has been widely recognized for its dedication to

			addressing unmet medical needs, earning acclaim for its extensive orphan drug portfolio.
10	Amryt Pharma plc	0.20	Amryt has rapidly grown its portfolio through strategic acquisitions and partnerships, offering therapies for epidermolysis bullosa and familial chylomicronemia syndrome. Notable achievements include obtaining FDA approval for Myalept®, the first therapy for treating generalized lipodystrophy, and advancing its pipeline with promising candidates targeting additional rare diseases.

Thus, we can summarize that the growth of the orphan drug market is fueled by two primary factors. First, the increasing identification and recognition of rare diseases, which has been significantly enhanced by advancements in diagnostic technologies such as next-generation sequencing, genetic testing, and biomarker research. These methods enable earlier and more accurate detection of rare diseases, leading to a rise in reported cases. Second, the market is bolstered by the active development of both innovative, cutting-edge therapies and generic alternatives to treat rare conditions. Pharmaceutical companies are investing heavily in research and development to address the unmet medical needs of patients suffering from orphan diseases. Additionally, supportive policies, such as government incentives and streamlined regulatory frameworks in regions like the United States and the European Union, further stimulate the development and availability of orphan drugs.

3.2. Identification of the main approaches to improving the pharmaceutical care of patients with rare diseases

The launch of orphan drugs on the market is associated with significant risks for each pharmaceutical company, primarily due to the significant costs of their development and the impossibility of predicting the profit from their sale. In turn, the absence of such drugs poses a significant burden on healthcare and society due

to the social, psychological and economic consequences described above. According to forecast data, orphan drugs will account for almost 20% of the total sales of prescription drugs by 2024, but such a significant share is due to high prices.

The annual cost of treatment of a patient with an orphan disease compared to the cost of treatment of non-orphan diseases according to US statistics is shown in Fig. 3.4 [24].

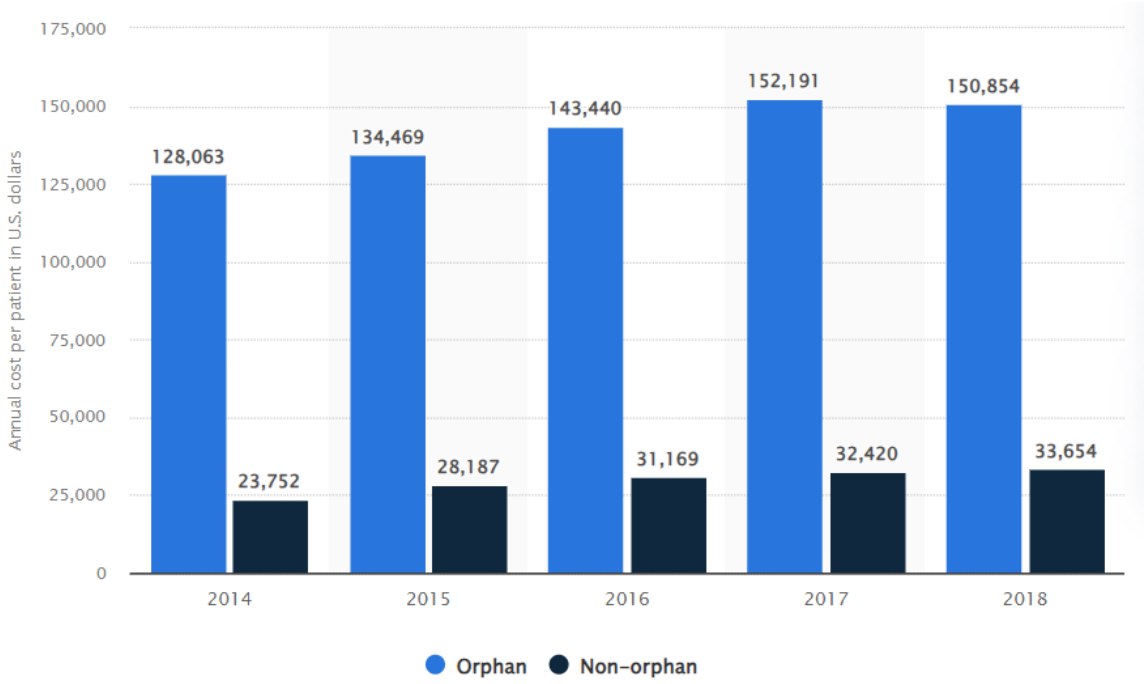

Fig. 3.4 Average annual cost of orphan drugs per patient (2014-2018)

As can be seen from these data, throughout the entire analysis period, the costs of drug therapy for patients with orphan diseases significantly exceed the costs of treatment with "traditional" drugs. For example, in 2018, this difference amounted to more than 117 thousand USD or more than 20%. In addition, it is noteworthy that in the period 2014-2018 there was a significant increase in the cost of treating one patient with orphan diseases - from 128 thousand USD to 150 thousand dollars, or by 18%. It should be noted that the cost of treating patients in the non-orphan group increased by 10 thousand USD or 41%.

A study of the cost of orphan drug treatment in the United States conducted by a group of authors [45] found that the use of FDA-approved drugs for the period 2017-2021 has significant costs for the treatment of patients with orphan diseases

and is several times higher than the cost of non-orphan therapy (table 3.2).

Table 3.2

Cost of treatment with new orphan drugs at market entry (2017–2021)

Non-Proprietary Name	Therapeutic Area	Duration of Therapy	Cost Per Year / Treatment at Market Entry, thousands USD
naxitamab-gqgk	Oncology	Cycles	1005,2
cerliponase alfa	Genetic Disorders	Chronic Use (1 year)	810,9
avalglucosidase alfa-ngpt	Oncology	Chronic Use (1 year)	634,7
lanadelumab	Other	Cycles	614,0
vestronidase alfa-vjbk	Genetic Disorders	Chronic Use (1 year)	600,6
tagraxofusp-erzs	Oncology	Cycles	527,0
emicizumab	Genetic Disorders	Chronic Use (1 year)	523,4
calaspargase pegol-mknl	Oncology	Cycles	511,4
ravulizumab-cwvz	Genetic Disorders	Chronic Use (1 year)	470,8
brexucabtagene autoleucel	Oncology	Single-use	460,2
evinacumab-dgnb	Genetic Disorders	Chronic Use (1 year)	399,3
elapegademase-lvlr	Genetic Disorders	Short treatment course	393,8
mogamulizumab-kpkc	Genetic Disorders	Cycles	369,1
teprotumumab-trbw	Other	Short treatment course	321,6
pegvaliase-pqpz	Genetic Disorders	Chronic Use (1 year)	280,7
burosumab-twza	Genetic Disorders	Cycles	280,2
inebilizumab-cdon	Genetic Disorders	Cycles	269,3
belantamab mafodotin-blmf	Oncology	Cycles	258,7
inotuzumab ozogamicin	Oncology	Cycles	258,2

asparaginase erwiniachrysanthemi (recombinant)-rywn	Oncology	Short treatment course	233,7
caplacizumab-yhdp	Genetic Disorders	Short treatment course	230,8
emapalumab-lzsg	Genetic Disorders	Cycles	230,8
satralizumab-mwge	Genetic Disorders	Chronic Use (1 year)	225,3
luspatercept-aamt	Genetic Disorders	Cycles	175,9
loncastuximab tesirine-lpyl	Oncology	Cycles	168,2
avelumab		Cycles	149,5
ibalizumab-uiyk	HIV	Chronic Use (1 year)	128,6
crizanlizumab-tmca	Genetic Disorders	Cycles	121,78
moxetumomab pasudotox-tdfk	Oncology	Cycles	114,368
cenegermin-bkbj	Genetic Disorders	Short treatment course	92,8
polatuzumab vedotin-piiq	Oncology	Cycles	85,4
tafasitamab-cxix	Oncology	Cycles	77,8
ropeginterferon alfa-2b-njft	Other	Chronic Use (1 year)	36,9

As was established in the previous stages of the analysis, the peculiarity of drug provision for patients with orphan diseases is the complexity of their diagnosis, precise determination of the duration of treatment and prognosis. As can be seen from the table, new orphan drugs are intended primarily for long-term use. In some cases, they are prescribed for use in cycles, in some - continuously. Only 6 new orphan drugs are intended for a short course and only 1 - for single use.

It was also determined that the cost of annual treatment with new orphan drugs averages 315,000 USD, with the maximum cost being over 1 million USD and the minimum being almost 40,000 USD. Only 4 orphan drugs out of 33 have an annual cost of less than 100,000 USD.

If we analyse the data on the cost of treatment of certain diseases, we can also

see that the minimum cost of an annual course is about 200 thousand USD. Such costs of drug therapy for orphan diseases are quite high and inaccessible for most patients. Therefore, it is important to finance these costs from sources other than the patients and their families.

Table 3.3

Cost of treatment orphan diseases

Orphan drug / INN	Orphan disease	Cost per year / treatment, thousands USD
Soliris / eculizumab	paroxysmal nocturnal haemoglobinuria (PNH)	409,5
Elaprase / idursulfase	Hunter syndrome (mucopolysaccharidosis II)	375,0
Naglazyme / galsulfase	mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)	365,0
Cinryze / C1 inhibitor (human)	angioedema (swelling) attacks	350,0
Myozyme / alglucosidase alfa	Pompe disease	300,0
Fabrazyme / agalsidase beta	Fabry disease	200,0
Cerezyme / imiglucerase	Gaucher disease	200,0

In summary, it can be said that in many countries, health systems and policies are not adequately equipped to meet the needs of patients with orphan diseases. Due to the small number of patients, these conditions often do not receive sufficient attention on public health agendas, resulting in insufficient funding and a lack of special programs. Given the high cost of treating patients with orphan diseases, they are often left to deal with their illness alone. As has been established, there may be no national orphan disease registries or programs that track the incidence and prevalence of these diseases. Naturally, without such data, it is difficult to effectively forecast and allocate public resources or attract other patient support programs. Governments may also lack the necessary structures to incentivize pharmaceutical companies to develop affordable orphan drugs, leaving patients without access to

potentially life-saving treatments.

Considering the peculiarities of the organisation of pharmaceutical care for patients with orphan diseases, it is possible to identify a system of factors that have both positive and negative effects on it. Positive factors include the advantages that patients with orphan diseases have in the organisation of pharmaceutical care, as well as positive opportunities for the organisation of such care at the level of the state and individual medical institutions. Negative factors include those that prevent the achievement of the goal of quality and timely provision of medicines to patients with orphan diseases, and impair this process at all levels.

Based on the results of the analysis, a grouping of the "weak" aspects of pharmaceutical care for patients with orphan diseases was carried out from the point of view of organisational and economic problems, and three groups of factors were formed – political, economic and social (Fig. 3.5).

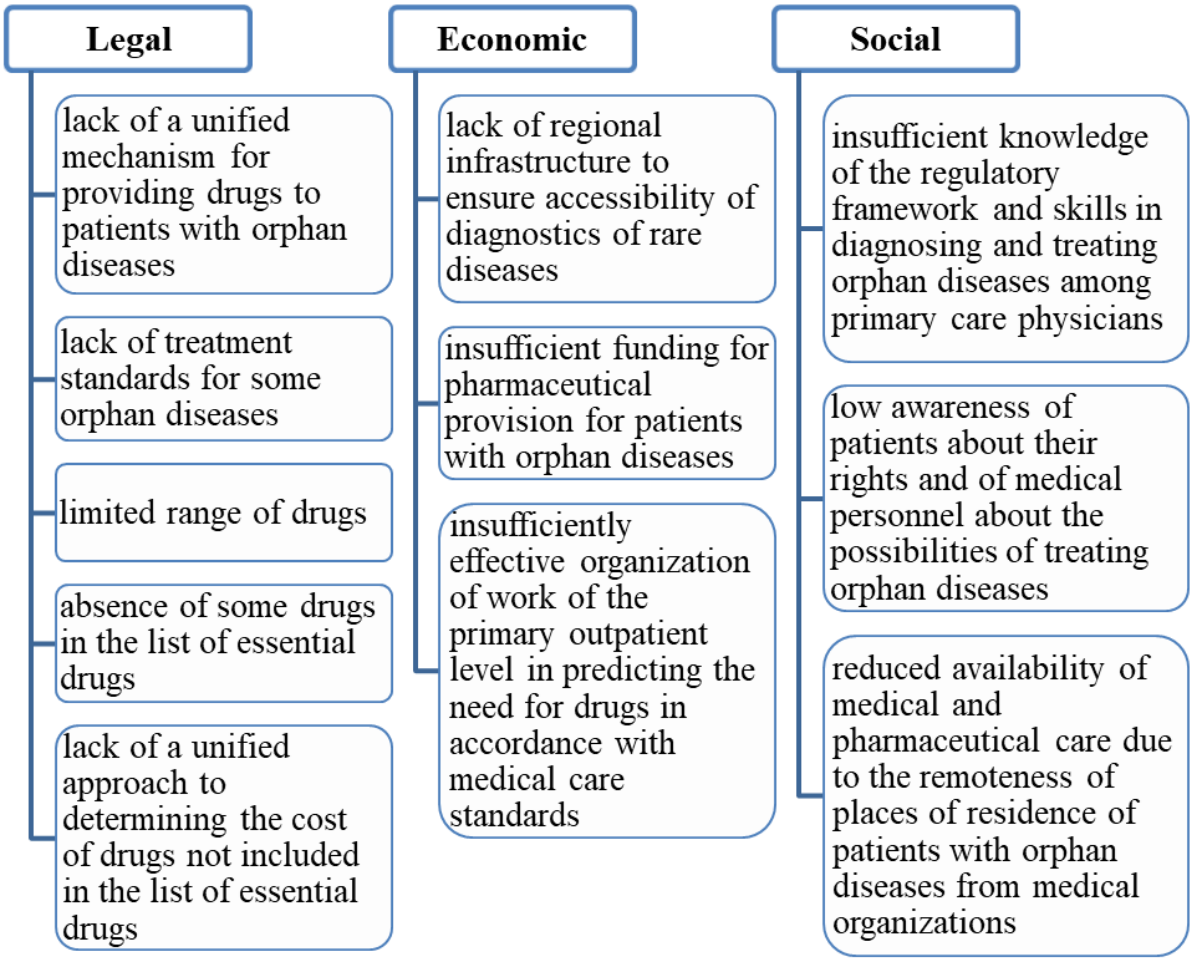

Fig. 3.5 Grouping of factors that negatively influence the state of drug supply for patients with orphan diseases

The structuring and grouping of factors having a negative impact on the organisation of pharmaceutical care for patients with orphan diseases made it possible to identify the following pattern - the maximum number of "weak" aspects of this process has a legal basis. The development and adoption by each country of regulatory documents on the organisation of the activities of the pharmaceutical supply system will increase the availability of medicines for patients with orphan diseases.

Based on the findings of the study, we have outlined key recommendations to enhance pharmaceutical care for patients with orphan diseases. These proposed directions include:

- development of a national programme on rare diseases. This programme should address critical aspects such as diagnosis, selective screening, medical care, and medical-social support for patients with rare diseases.
- fostering national and international collaboration. Strengthening partnerships in the fields of diagnosis, treatment, and prevention of rare diseases to improve outcomes and share expertise.
- comprehensive data collection. Establishing mechanisms for gathering statistical information on the prevalence and spectrum of rare diseases at both national and international levels.
- creation of a national rare disease patient registry. This will help centralise patient data, ensuring accurate tracking and improved management of rare disease cases.
- advancement of early diagnosis techniques. Developing and implementing efficient methods for the early identification of rare diseases to enable timely intervention.
- effective treatment and rehabilitation approaches. Introducing innovative and evidence-based treatment methods to reduce the rates of mortality and disability among rare disease patients.
- specialist training programmes. Providing comprehensive training for

healthcare professionals in the diagnosis, treatment, and management of rare diseases, leveraging expertise from leading centres.

- increased awareness. Enhancing the knowledge of healthcare professionals across various specialities and educating patients about rare diseases to ensure better understanding and care.

To improve the pharmaceutical supply and increase both the physical and economic accessibility of orphan drugs, it is essential to create an environment that encourages collaboration between orphan drug manufacturers and government authorities or healthcare institutions at the national level. The measures should be implemented and regulated at the state level. For example, providing benefits to orphan drug manufacturers, such as exemptions from customs duties and other financial incentives to encourage production and distribution within the country. Also granting extended and exclusive rights for the sale of orphan drugs for a period of 10-15 years to incentivise innovation and market stability. Additionally, orphan drug list and pricing policies – establishing an official list of orphan drugs with regulated supply levels and caps on profit margins to make them more affordable and accessible to patients in need.

Therefore, in order to implement the established directions for improving pharmaceutical care for patients with orphan diseases, an integrated approach is required, starting with the definition of legal, economic and social problems at the country level and the approach to solving them in accordance with the available resources.

Conclusions to chapter 3

Statistical data on the change in the cost of pharmacotherapy for patients with orphan diseases compared to the cost of treatment with non-orphan drugs were analysed. It was found that the annual cost of treating a patient with orphan drugs varies from 30 000 USD to more than 1 million USD. The cost of annual treatment for the most common diseases is more than 300 000 USD.

The formed problem areas in pharmaceutical care of patients with orphan diseases allowed us to group the factors of negative impact on the organisation of pharmaceutical care of patients with orphan diseases, to identify problem areas in the organisation of care of this category of patients, to establish the shift of "threats" towards financial dependence of the process of pharmacotherapy in connection with significant costs of orphan drugs.

Measures have been proposed to improve the physical and economic accessibility of orphan drugs and to ensure an increase in the level of pharmaceutical cfre to orphan disease patients.

GENERAL CONCLUSIONS

1. The analysis of scientific articles and statistical reports on orphan diseases, their diagnosis and treatment consequences is carried out. It is established that orphan diseases are rare congenital or acquired diseases that chronically progress, worsen the quality of human life and lead to its reduction, the frequency of which is very low among the population (not exceeding five cases per 10 thousand people). The term orphan disease was first introduced in 1983 (USA).
2. It is recognised that orphan diseases are an urgent problem for modern health care and society as a whole. At present, there is no uniform approach to their classification and the establishment of epidemiological indicators. It is noted that in many countries orphan diseases are recognised as an independent class of diseases, the criterion of prevalence of these diseases at the national level is established, which differs from that in other countries.
3. To encourage the development and production of drugs to treat orphan diseases, many countries have introduced accelerated approval procedures, tax incentives and exclusive marketing rights. Programmes to support patients with orphan diseases are also being developed. However, the number of such programmes does not fully meet the needs of patients in this category.
4. Regulatory and legal approaches to the organisation of pharmaceutical provision for patients with orphan diseases in different countries of the world are analysed.
5. The data on the structure of the market for orphan drugs by groups of orphan diseases, by countries of the world, and by manufacturers was analysed. The main directions in the development of orphan drugs by leading pharmaceutical manufacturers in this market segment were identified.
6. Data on the cost of treating patients with orphan drugs has been analysed on a year-by-year basis and compared with the cost of treating patients with non-orphan drugs. It was found that the average annual cost of treating a patient

with the most common orphan diseases is 300,000 USD. The cost of treating a patient with new orphan drugs that have entered the market in recent years ranges from 30,000 USD to 1 million USD per patient per year.

7. A typology of problem areas in the pharmaceutical care of patients with orphan diseases was developed and the most negative political, economic and social factors were identified.
8. Ways to improve the physical and economic accessibility of orphan drugs for patients are proposed, which will improve the level of pharmaceutical care for patients with orphan diseases.

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Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of social pharmacy
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Social Pharmacy

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Alina VOLKOVA
"15" of April 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION
Fatima Zahra TALBAUI

1. Topic of qualification work: «A study on the organization of pharmaceutical care for patients with orphan diseases»
supervisor of qualification work: Alla KOTVITSKA, D.Sc. in Pharmacy, professor
approved by order of NUPh from "06th" of February 2024 № 34

2. Deadline for submission of qualification work by the applicant for higher education: October 2024.

3. Outgoing data for qualification work: morbidity and prevalence rates; regulatory documents governing the provision of medicines to patients with orphan diseases; analytical data.

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
- to analyse scientific sources of information on rare diseases;
- to study the prevalence of orphan diseases in the world population;
- to examine the challenges of providing pharmaceutical care to patients with orphan diseases worldwide;
- to analyse government regulatory practices for the pharmaceutical care of patients with orphan diseases;
- to assess the pharmaceutical market for drugs used in the treatment of orphan diseases;
- to evaluate strategies to improve the organisation of pharmaceutical care for patients with orphan diseases.

5. List of graphic material (with exact indication of the required drawings):
Tables – 5, figures – 8

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Alla KOTVITSKA, professor of the Social Pharmacy Department	16.04.24	16.04.24
2	Alla KOTVITSKA, professor of the Social Pharmacy Department	24.04.24	24.04.24
3	Alla KOTVITSKA, professor of the Social Pharmacy Department	25.04.24	25.04.24

7. Date of issue of the assignment: «15» of April 2024

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Analysis of orphan diseases as a medical and social problem	April 2024	done
2	Analysis of the principles of pharmaceutical support for patients with orphan diseases in the world.	April 2024	done
3	Analysis of the legal framework for the regulation of orphan drugs worldwide.	May 2024	done
4	Analysis of the current state of the market for orphan drugs.	May - June 2024	done
5	Identification of the most important approaches for the improvement of the pharmaceutical support of patients with rare diseases.	June 2024	done
6	Summary of the results of the study	September 2024.	done
7	Finalizing the work, preparing the report	October 2024	done

An applicant of higher education Fatima Zahra TALBAUI

Supervisor of qualification work Alla KOTVITSKA

ВИТЯГ З НАКАЗУ № 34
По Національному фармацевтичному університету
від 06 лютого 2024 року

1. Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу 2 циклу Фм20*(4,10д) 2024-2025 навчального року, ступінь вищої освіти «магістр», галузь знань 22 Охорона здоров'я, спеціальність 226 – Фармація, промислова фармація, освітньо-професійна програма – Фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців). Мова навчання англійська

№ з/п	Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі соціальної фармації**					
19.	Талбауі Фатіма Захра	Дослідження організації фармацевтичної допомоги пацієнтам з орфанними захворюваннями	A study on the organization of pharmaceutical care for patients with orphan diseases	професор Котвіцька А.А.	Професор Малий В.В.

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«20» листопада 2024 р. № 329631365

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Талбауі Фатіма Захра, Фм20*(4,10д)-англ-02, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Дослідження організації фармацевтичної допомоги пацієнтам з орфанними захворюваннями / A study on the organization of pharmaceutical care for patients with orphan diseases», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Fatima Zahra TALBAUI

on the topic: "A study on the organization of pharmaceutical care for patients with orphan diseases"

Relevance of the topic. Orphan diseases require special attention not only from the medical community but also from society as a whole, as their diagnosis, prevention and treatment represent some of the most complex problems in practical healthcare. Patients face many difficulties, ranging from the high cost of treatment to social isolation. From an economic point of view, orphan drugs are expensive, the diseases are costly, and the number of patients is constantly increasing, according to some reports by 10-13% per year, partly due to the expansion of the diagnostic armamentarium. Addressing these issues requires a systematic approach, including the development of government programmes, support for research and the involvement of patients with rare diseases. Therefore, the choice of the topic of the research is relevant.

Practical value of conclusions, recommendations and their validity. The results of the research can be used as a basis for the development of a series of organisational and economic approaches to improve pharmaceutical care for patients with orphan diseases.

Evaluation of the work. During the research Fatima Zahra TALBAUI showed the ability to practically use modern scientific methods of research, to draw conclusions based on the analysis. The work is of a sufficient scientific standard.

General conclusion and recommendations for admission to the defence In general, the qualification work of the applicant for higher education Fatima Zahra TALBAUI on the topic "A study on the organization of pharmaceutical care for patients with orphan diseases" is carried out at the appropriate level, meets the requirements for qualification works "Regulations on the procedure for the preparation and defence of qualification works at the National University of Pharmacy" POL A2.2-32-025 (ed. 04-2021) from 26.08.2021 and can be recommended for defence at the Examination Commissions of the National University of Pharmacy.

Supervisor _____ Alla KOTVITSKA

«07» November 2024

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Fatima Zahra TALBAUI

on the topic: "A study on the organization of pharmaceutical care for patients with orphan diseases"

Relevance of the topic. Orphan diseases are not only a medical problem, but also a profound social issue that affects the lives of patients on many levels. Due to the rarity and often severe impact of these diseases, patients often face unique obstacles in their daily lives and require continuous and comprehensive medical and social support. In turn, the provision of orphan drugs to patients with rare diseases entails significant financial costs for governments and patients, mainly due to the high cost of the orphan drugs themselves, which is a result of the substantial financial investment in their development and production, combined with low sales volumes due to the small size of the target patient population.

Theoretical level of work. The structure and content of the qualification work are traditional. The qualification work is based on the study of scientific literature sources, processing and analysis of statistical data on the declared subject. These analyses are logically systematised and reflected in the text of the paper.

Author's suggestions on the research topic. Based on the results of the analysis, approaches to improve the provision of pharmaceutical care for patients with orphan diseases were proposed.

Practical value of conclusions, recommendations and their validity. The review of the qualification work provides grounds for asserting the practical value of the proposed recommendations, which are based on applied results and can be used to improve approaches to the provision of pharmaceutical care to patients with orphan diseases.

Disadvantages of work. There are numerous stylistic errors and typos in the text, which does not affect the overall grade.

General conclusion and evaluation of the work. According to the relevance and the results of the research, qualification thesis meets the requirements for a qualification thesis and can be recommended for official defence before the Examination Commission Board of the National University of Pharmacy.

Reviewer _____ D.Sc. in Pharmacy, professor Volodymyr MALYI

«08» November 2024

ВИТЯГ
з протоколу засідання кафедри соціальної фармації
№ 5 від «08» листопада 2024 року

ПРИСУТНІ: зав. каф. доц. Аліна ВОЛКОВА, проф. Ганна ПАНФІЛОВА, проф. Вікторія НАЗАРКІНА, доц. Галина БОЛДАРЬ, доц. Наталія ГАВРИШ, доц. Тетяна ДЯДЮН, доц. Юлія КОРЖ, асист. Альміра НОЗДРІНА, доц. Вікторія МІЩЕНКО, доц. Ірина ПОПОВА, доц. Олександр СЕВРЮКОВ, доц. Ірина СУРІКОВА, доц. Любов ТЕРЕЩЕНКО, доц. Наталія ТЕТЕРИЧ.

ПОРЯДОК ДЕННИЙ:

Про представлення до захисту в Екзаменаційній комісії кваліфікаційних робіт.

СЛУХАЛИ: завідувачку кафедри доц. Аліну ВОЛКОВУ з рекомендацією представити до захисту в Екзаменаційній комісії кваліфікаційну роботу здобувача вищої освіти спеціальності 226 Фармація, промислова фармація Талбауі Фатіми Захри на тему: «Дослідження організації фармацевтичної допомоги пацієнтам з орфанними захворюваннями».
Науковий керівник д. фарм. н., проф. Алла КОТВІЦЬКА.
Рецензент д. фарм. н., проф. Володимир МАЛИЙ.

УХВАЛИЛИ: Рекомендувати до захисту в Екзаменаційній комісії кваліфікаційну роботу здобувача вищої освіти Талбауі Фатіми Захри на тему: «Дослідження організації фармацевтичної допомоги пацієнтам з орфанними захворюваннями».

Завідувачка каф. СФ, доцент Аліна ВОЛКОВА

Секретар, доцент Наталія ТЕТЕРИЧ

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувачка вищої освіти Талбауі Фатіма Захра до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Дослідження організації фармацевтичної допомоги пацієнтам з орфанними захворюваннями» (A study on the organization of pharmaceutical care for patients with orphan diseases)

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Під час виконання кваліфікаційної роботи здобувачка вищої освіти Талбауі Фатіма Захра опрацювала достатню кількість літературних джерел за тематикою дослідження, а також проаналізувала звіти й аналітичну інформацію з досліджуваних питань. Здобувачка показала уміння аналізувати дані, узагальнювати результати дослідження та робити висновки. Усі поставлені завдання відповідно до мети роботи виконано у повному обсязі. Результати дослідження належним чином представлені у вигляді рисунків та таблиць.

Таким чином, кваліфікаційна робота може бути рекомендована до офіційного захисту в Екзаменаційній комісії Національного фармацевтичного університету

Керівник кваліфікаційної роботи

_____ Алла КОТВІЦЬКА

«07» листопада 2024 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувачка вищої освіти Талбауі Фатіма Захра допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
соціальної фармації

_____ Аліна ВОЛКОВА

«08» листопада 2024 року

Qualification work was defended

of Examination commission on

“28” November 2024

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /