ОРГАНІЗАЦІЙНІ ТА СОЦІАЛЬНО-ЕКОНОМІЧНІ ЗАСАДИ ФАРМАЦЕВТИЧНОЇ ДІЯЛЬНОСТІ

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THE IMPORTANCE OF LEGISLATION IN DEVELOPING ORPHAN DRUGS

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The aim of this study is to conduct the analysis of legislation in the field of orphan drugs in world practice. The review of literature has shown that significant achievements in research and development of orphan drugs have really begun only after adopting different laws and regulations followed by development of therapies for rare diseases. About 7000 rare diseases affect over 350 million people worldwide and have a negative impact on patients and their families. The research and development in the field of orphan drugs are difficult processes because of the lack of understanding the mechanism of the disease and due to the high cost of these processes. Therefore, to encourage the research in this field many countries have developed and implemented legislations that offer stimuli, support and assistance to drug manufacturers, starting with the formulation of these drugs up to receiving the marketing authorization. The Orphan Drug Act was firstly adopted in the United States in 1983. As a result, in the first ten years, 620 drugs became orphan, and 87 received the marketing authorization. Following the great impact of this act, Japan, Australia and the European Union later adopted such policies. Currently, 89 orphan drugs covering 12 ATC groups have been authorized in Europe.

Key words: rare diseases; orphan drugs; orphan drugs legislation; orphan drugs development.

Statement of the problem. Rare diseases are a complex and heterogeneous mosaic of 7000 conditions that affect over 350 million people worldwide; they are frequently life-threatening or chronically debilitating, and the impact on the quality of life of affected patients and their family members is thus significant [2, 25, 30, 34]. About 80% of these rare diseases have the identified genetic origin. The others are caused by infections, allergies, or are due to degenerative, proliferative or teratogenic causes. Some rare diseases are also caused by a combination of genetic and environmental factors [13]. A rare disease or an "orphan" disease is defined as one that affects a restricted number of people and has no effective treatments. There are different definitions of a rare disease and they may differ among countries, but the common criterion is the low prevalence of the disease (Table 1) [5, 10, 28].

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Table 1

THE DEFINITION OF A RARE DISEASE AMONG COUNTRIES

Country	Prevalence	The number of affected people
United States of America	7.5:10 000	< 200 000
Japan	4:10 000	< 50 000
Australia	1.2:10 000	< 2000
Europe	5:10 000	< 250 000

Table 2

THE INTERNATIONAL ORPHAN DRUG LEGISLATION

Country/ region	Legislation	Year of passing
USA	Orphan Drug Act	1983
Japan	Orphan Drug Regulation	1993
Australia	Australian Orphan Drugs Program	1997
European Union	Regulation No. 141/2000	2000

The "orphan drug-movement" is believed to have been initiated with the Orphan Drug Act of 1983 in the United States of America. Actually, in 1851 the well-known Flemish physician Rembert Dodoens wrote *"Medicinalium observationum exempla rara"*, a book about the diagnosis and treatment of rare diseases. In the book 200 rare diseases of the 16th century such as *Aneurisma, Calculus in vesica, Catalepsis, Dysenteria, Tetanos, Vomitus sanguinis* were described. For pharmacological treatment Rembert Dodoens referred to his own book of herbs from 1554, *"Cruydenboeck", w*ith *"Plaetse, Tijt, Naem, Natuere, Kracht ende Werckinghe"*, representing the growing place and time, the name, identification and the pharmacological activity of 942 plants. At the end of some monographs the operating procedures for production of "orphan drugs" from the plant raw material are given [6].

Orphan drugs are medicines intended to treat, prevent or diagnose a rare disease. Availability and access to medicines are important to reduce morbidity and mortality of rare diseases. Despite the need and importance of availability and access to orphan drugs there is the lack of available treatments for rare diseases. Less than one in ten patients with rare disease receives a disease-specific treatment [9].

The aim of the study is to conduct the analysis of legislation in the field of development of orphan drugs.

Material and methods. This study is a review of orphan drug legislation in the most representative states. For the study 34 references from PubMed and SpringerLink platform and Orphanet web page were chosen.

Results. The drug development for rare diseases is limited by the lack of understanding of the underlying mechanisms of the disease and by the high costs of research and development (~$1 billion) [11] that cannot be subsequently covered. This situation dates back to the 1960s when following the thalidomide tragedy all drugs must be shown to be safe and effective through "adequate and well-controlled studies" before receiving the market approval. This condition raised the cost of drug development, and the rare disease population became a vulnerable one, being 'orphaned' by many major drugs. And, therefore, the problem of treatment for rare diseases became very real [12, 34].

Therefore, in several jurisdictions, specific legislation and policies have been introduced to stimulate development of orphan drugs (Table 2) [9, 20].

United States of America. In 1978, after years of discussion and concern, a task force created by what is now the U.S. Department of Health and Human Services issued a call for action in a report on what might be done to promote development of drugs with the limited commercial value. Later, after the Congress held hearings (1980-1982) about problems of drugs for rare diseases, in 1983 the Orphan Drug Act (ODA), the first significant public commitment by any nation to promote development of drugs for people with rare diseases, was signed. The same year the US Food and Drug Administration (FDA) approved the first two orphan drugs [8].

According to the ODA, orphan drugs are intended for treating "any disease or a condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" [24].

Only in the first 10 years, 620 drugs received an orphan designation and 87 drugs received a marketing approval [31], in contrast with only 10 treatments approved in 8-10 years prior to the orphan drug legislation [34]. In the first 25 years of the ODA in the USA 1892 products were designated as orphan, and 326 products for more than 200 rare diseases were approved [25]. Since the passage of the ODA nearly 500 orphan drugs were approved, with 233 of those approvals in the last decade alone, more than 230 new orphan drugs were approved by the FDA [1]. At the end of 2014 the FDA granted the orphan drug designation to 3273 potential therapies [32].

Japan. The success of the ODA inspired later other states concerned with supporting patients suffering from rare diseases. So, on the 1st of October, 1993, the Japanese government revised the pharmaceutical law by introducing special provisions relative to research and development of orphan drugs. According to these new provisions, the orphan drug status is granted by the Ministry of Health, Labor and Welfare only when the drug meets the following two criteria [23]:

1. the drug is intended for an incurable disease with no possible alternative treatment, or the efficacy and the expected safety of the drug must be excellent compared to other available drugs;

2. the number of patients affected by this disease in Japan must be less than 50000 on the Japanese territory.

Similar to the USA, the Japanese orphan drugs system offered new opportunities both for multinational and small-size and medium-size companies that in the first 10 years obtained the marketing authorization for 94 drugs and devices [19]. In 2015, 246 drugs among 323 orphan designated drugs received the marketing approval [15].

Australia. The Australian orphan drugs policy was set up in 1997. This orphan drugs program aims to ensure the availability of treatments for rare diseases and allows the Australian Therapeutic Goods Administration to use information from the FDA Orphan Drugs Program as part of the Australian evaluation process. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of 2000 patients or less in the Australian population or drugs are not commercially viable when used in the patient population they are indicated for [22]. As a result, 287 drugs were designated as orphan and 144 drugs received the marketing authorization by 2013 [17].

European Union. Rare diseases were firstly identified as a priority area for the Community action in November, 24, 1993, in the communication of the Commission. The experience has shown that by the very fact of their rareness and the consequent lack of the available information about them rare diseases can produce significant problems for individual countries [3]; the diagnosing process and identification of an available treatment of rare diseases need an added value at the European level. To achieve this goal the European Parliament and the Council adopted Regulation No 141/2000 on orphan drugs in December, 16 1999. The so-called orphan drugs are defined as [27]:

1. medicinal products intended for the diagnosis, prevention and treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made;

2. medicinal products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

3. medicinal products intended for diseases for which there is no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

This regulation, is largely inspired by the U.S. regulation and its goals are [16, 27]:

- to encourage the pharmaceutical and biotechnological industry to carry out research and development of orphan drugs;
- to involve competent small and medium-size enterprises for participation in this development in special sectors;
- to create a Committee of Orphan Medicinal Products that is responsible for studying the applications for orphan designation

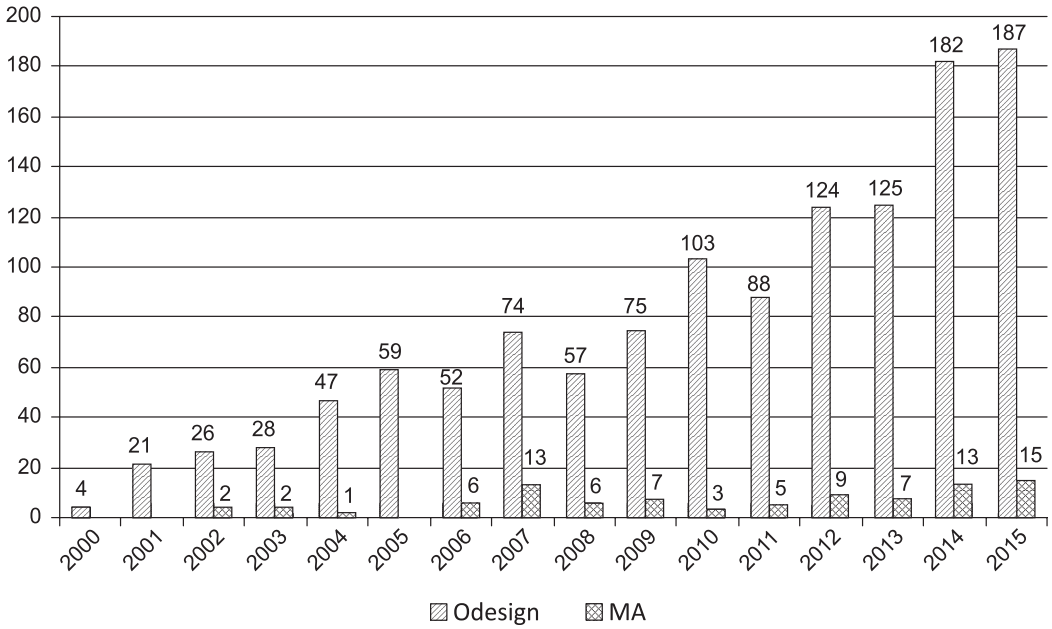

Fig. 1. The number of orphan designated medicinal products and orphan medicinal products with the marketing authorization in the EU

within the European Medicines Evaluation Agency and to advise and assist the Commission in discussions on orphan drugs;

- to increase the knowledge on these diseases, their environment, improve communication and cross-border collaboration between the various research centers, institutions, patients.

In April, 27, 2000, the European Commission adopted the regulation No 847/2000 determining such criteria of orphan designation as the rarity of the disease and the life-threatening conditions [4].

In the framework of these regulations during 15 years 1253 medicinal products [26] of 2385 applications [18] received orphan designation in EU. However, the large number of designated orphan drugs may provide false hope to patients with rare diseases because only a small percentage of these designated orphan drugs have obtained the marketing approval [2]. Thus, till now, 102 orphan medicinal products were submitted for obtaining the marketing authorization, and there were 89 of those that received the marketing authorization (Fig. 1).

Orphan medicinal products with the marketing authorization cover 12 ATC groups: A – Alimentary tract and metabolism, B – Blood and blood forming organs, C – Cardiovascular system, D – Dermatologicals, H – Systemic hormonal

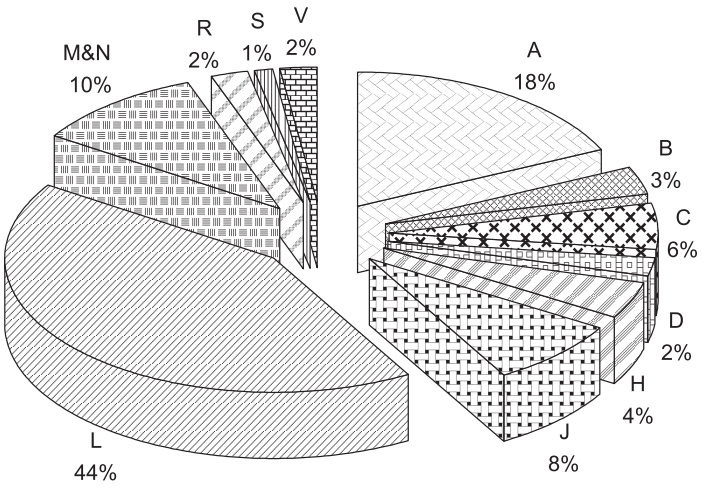

Fig. 2. Distribution of authorized orphan medicinal products by ATC groups

Table 3

ORPHAN DRUG INCENTIVES IN DIFFERENT COUNTRIES

Parameters	USA	Japan	Australia	EU
Marketing exclusivity	7 years	10 years	5 years (similar to other drugs)	10 years
Tax credit	Yes: 50% for clinical studies	Yes: 6% for any type of the study + limited to 10% of the company's corporation tax	No	Managed by the member states
Grants for research	Programs of NIH and others	Governmental funds	No	"FP6" + national measures
Reconsideration of applications for orphan designation	No	Yes	Yes (every 12 months)	Yes (every 6 years)
Technical assistance for elaboration of the application file	Yes	Yes	No	Yes
Accelerated marketing procedure	Yes	Yes	Yes	Yes (via the centralized procedure)

preparations, J – Antiinfectives for systemic use, L – Antineoplastic and immunomodulating agents, M – Musculo-skeletal system, N – Nervous system, R – Respiratory system, S – Sensory organs, V – Various (Fig. 2).

Despite development of orphan drugs only about 2% of the rare diseases identified are currently covered by approved treatments [33], and the cost of orphan drugs is still high, commonly exceeding $100000 per a patient a year [7]. Even so, the orphan drug legislation elsewhere has been incredibly successful in promoting development of new treatments for rare diseases [21], especially because of different and attractive incentives (Table 3) [10, 29].

Conclusions

Rare diseases represent a key challenge to the healthcare system. With less than 2% of the identified rare diseases currently covered by approved treatments the rare disease population is underserved both clinically and scientifically [14, 33]. Under human rights principles, patients with rare diseases have equal rights to medicines as other patients with more prevalent disease [9].

Although the rarest diseases have no available treatment, the last 30 years have shown that rare diseases represent an accessible field for research and development with a great potential in discovering the necessary medicines and achieving commercial success.

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ВАЖНОСТЬ ЗАКОНОДАТЕЛЬСТВА ПРИ РАЗРАБОТКЕ ОРФАННЫХ ЛЕКАРСТВЕННЫХ СРЕДСТВ

Е. Згырку

Целью исследования стало проведение анализа законодательства в области орфанных лекарственных средств в мировой практике. Обзор литературы показал, что значительные достижения в области исследований и разработки орфанных препаратов начались только после принятия различных законов и нормативных актов с целью способствования развитию терапии редких заболеваний. Во всем мире более 350 млн человек страдают от около 7000 редких заболеваний, которые оказывают негативное влияние на пациентов и их семьи. Исследования и разработка орфанных препаратов являются сложными процессами из-за недостатка понимания механизма заболевания и их высокой стоимости. Для стимулирования деятельности в исследуемой области многие страны разработали и внедрили законодательные акты, которые стимулируют производителей, предлагают им поддержку и помощь, начиная от разработки таких препаратов и заканчивая получением разрешения на их реализацию. Закон об орфанных препаратах впервые был принят в США в 1983 г. В течение первых десяти лет 620 препаратов получили статус орфанных и 87 – разрешение на реализацию. Этот акт имел значительное влияние, поэтому Япония, Австралия, а позже и Европейский Союз приняли такую же политику. В настоящее время в Европе получено разрешение на реализацию 89 орфанных лекарственных средств, которые охватывают 12 АТС групп.

Ключевые слова: редкие заболевания; орфанные лекарственные препараты; законодательство; разработка орфанных препаратов.

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ВАЖЛИВІСТЬ ЗАКОНОДАВСТВА ПРИ РОЗРОБЦІ ОРФАННИХ ЛІКАРСЬКИХ ЗАСОБІВ

Е. Згирку

Метою дослідження стало проведення аналізу законодавства у сфері орфанних лікарських засобів у світовій практиці. Огляд літератури показав, що вагомі досягнення у сфері досліджень і розробки орфанних препаратів почалися тільки після ухвалення різних законів і нормативних актів з метою сприяння розвитку терапії рідкісних захворювань. У всьому світі понад 350 млн осіб страждають від близько 7000 рідкісних захворювань, які негативно впливають на пацієнтів і їх родини. Дослідження і розробка рідкісних препаратів є складними процесами через недостатнє розуміння механізму захворювання та їх високу вартість. Для стимулювання діяльності в досліджуваній сфері багато країн розробили й упровадили законодавчі акти, які стимулюють виробників, надають їм підтримку і допомогу, починаючи від розробки таких препаратів і закінчуючи отриманням дозволу на їх реалізацію. Закон про орфанні ліки вперше був ухвалений у США у 1983 р. Протягом перших десяти років 620 препаратів отримали статус орфанних і 87 – дозвіл на реалізацію. Цей акт мав значний вплив, тому Японія, Австралія, а пізніше і Європейський Союз прийняли таку саму політику. На сьогодні в Європі отримано дозвіл на продаж 89 орфанних лікарських засобів, які охоплюють 12 АТС груп.

Ключові слова: рідкісні захворювання; орфанні лікарські препарати; законодавство; розробка орфанних препаратів.