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Orphan diseases, orphan drugs and orphan regulation in USA and EU

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Abstract:-No single definition for an orphan diseases exists worldwide, but it is generally a disease that affects a small portion of the world population. Despitethe development of science and pharmaceutical technology, the number of rare diseases for which no treatment is available is estimated between 4.000 and 5.000 worldwide. Theanalysis of the finances that are required for research, development and manufacturing of orphan drugssuggest that these drugs are perhaps the most expensive drugs produced by the pharmaceutical industry.
The main objective of orphan regulations is to encourage pharmaceutical companies to begin the process of researching and developing of new drugs intended for treatment of orphan diseases. The first legal framework for defining the rules for the marketing authorization of the orphan drugs waspresented by the Food and Drug Administration (FDA) in the 1983.In EuropeanUnion, the regulation fororphan drugs was introducedby the EuropeanMedicinesAgency (EMA) in1999.The FDA orphan drugs regulation is based on three laws, while the EUlegislation is covered by six regulations and two additionalguidelines.The detailed overview of the FDA and EMA orphan drugs regulatory requirements showed that both regulatory authorities provideshortened registration procedure, allow exception from payment of certain fees, provide protocol assistance and stimulate processes of a parallel application for orphan designation. The differencescould be seen in the period of market exclusivity, taxincentives and source of the grants.

Keywords:-*Incentives, orphan (rare) diseases, orphan drugs, orphan drugs regulation*

I. INTRODUCTION

Generally, orphan (rare) diseases are considered to be severe, progressive, degenerative, life-threatening or chronically debilitating diseases with a low prevalence[1].The definition of orphan diseases is in accordance with different legislation, procedures and national regulations, but generally speaking these diseases affect a relatively small portion of the world population.Genetic factors, allergies, infections (bacterial or viral), degenerative or proliferative processes in combination with other environmental factors (chemical agents or radiation) or a combination of genetic factors and environmental factors, are considered as a fundamental and the most common causes of rare diseases[2-4].

According to the definition by the World Health Organization (WHO), an orphan disease is an illness or condition that occurs from 0.65 to 1 case per 1000 population, with a prevalence from 6.5 to 10 cases per 10.000 residents.Up to date, there are found to be between 6.000 to 8.000 known orphan diseases, with almost weekly reporting of newly identified disorders. Annually, approximately 250 new orphan diseases are identified [1].Despite the fact that orphan diseases affect a small portion of the world population, it is estimated that over 55 million people suffer from orphan diseases at the level of the United States (USA) and European Union (EU). In the USA there are about 25 million people who suffer from an orphan disease, while at European level about 30 million people are registered with orphan diseases, meaning that orphan diseases affect 6% to 8% of the population at European level [5]. The large part of orphan diseases (about 50%) appear during early childhood. Approximately 80% of the known orphan diseases have been identified as genetic in nature affecting between 3% and 4% of the newborns[6].

Orphan drugs are defined as drugs that are used for treatment oforphan(rare)diseases.Theanalysis of the finances thatare required for research, development and manufacturing of orphan drugssuggest that these drugs are perhaps the most expensive drugs produced by the pharmaceutical industry[7].For illustrations,the cost for orphan drugs per patient in the USA for 2014was $ 118.820,00, versus the cost of$ 23.331,00for non-orphan drugs for the same period[8].

The registration of orphan drugs is in accordance with the special legislation, in literature known as an orphan regulation.The main goal of the orphan regulation is to stimulate the pharmaceutical companies to begin the process of research and production of orphan drugs.Worldwide, the most frequently referred regulations for orphan drugs are regulations setby the Food and Drug Administration(FDA) and European Medicines Agency (EMA) in theUSAand EU, respectively.

II. ORPHAN DRUG REGULATION IN USA AND EU

The definition for orphan drugs is in line with the definition for orphan diseases at national level. This means that a drug could receive orphan designation only if it is intended for treatment of patients who suffer from some orphan disease according to national definition for orphan diseases.In the USA some drug may be designated as an orphan drug although it is intended for treatment of larger number of patients, over the allowed limit of number of patients(Table 1). However it should be proven that there is no reasonable expectation that the cost for development and manufacturing of this drug would be recovered from it sales[9].

Table 1 Orphan diseasesdefinition in USA and EU

Country	**Total population**	**Prevalence of the rare diseases**	**Minimum number of patients necessary for being accepted as an orphan disease**
USA	311.864.524,00	6.4 / 10.000 residents	Less than 200.000 or more than 200.000 but there are not reasonable expectation that the costs for research and development of the drug will be recovered
EU	502.500.000,00	5 / 10.000 residents	Less than 251.250 patients

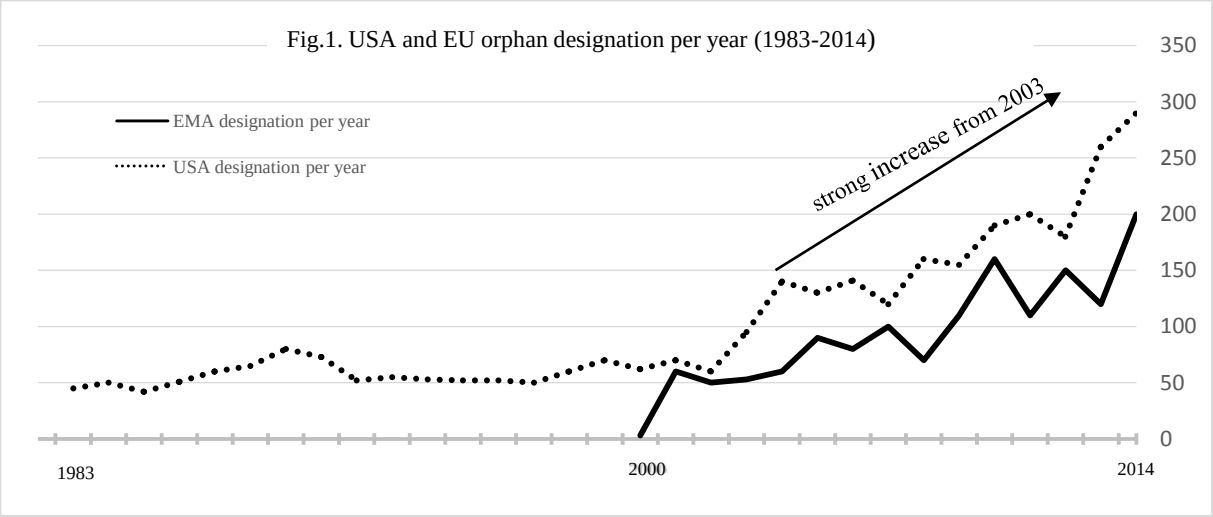
The high price of orphan drugs is due to the negative correlation between the high costs needed for research and their development and theprojected relatively small return of the investment from the sale of these drugs, according to a relatively small number of patients that will use these orphan drugs. On the other hand, this high cost is a limitation factor for availability of the product for the small group of alreadyexisting and targeted patients.According to the pharmaceutical companies' reports, approximately 21 billion dollars are needed for research and development of a medical treatment. In other terms, it means that about 10 years are needed for a new drug to be released on the market. Reference these economic parameters, the treatment of rare diseases is often characterized as "orphaned" and it is very rarely recognized as a field of interest by the pharmaceutical companies.Comparative data for top 100orphan drugs in USA by sales average and median cost per patient foryears 2010-2014 are presented in Table 2. The cost per patient was estimated for the retail cost of a drug to a patient, for a given year, based on a 100% compliance to the treatment guidelines outlined in the FDA label and it does not include off-invoice discounts [8].

Table 2 Average cost per patient ($)per year (2010 – 2014) for orphan drugs in USA

Average Cost per Patient ($) per year	**2010**	**2011**	**2012**	**2013**	**2014**
Orphan drugs	83.550	87.990	97.379	107.316	111.820
Growth per Year		5.3%	10.7%	10.2%	4.2%
Median price	37.767	42.329	50.352	63.435	66.057

Reference these data it could be concluded that the total growth for 4 years, in average cost per patient, for orphan drugs was 30,4% and growth in median price was 28.290$.

Despite the development of the medical science and the fast progress of the pharmaceutical industry, about 55% to 65% or 4.000 to 5.000 of the known rare diseases are still without anappropriate medical treatment [10].The main objective of orphan regulations is to encourage pharmaceutical companies to begin the process of researching and developing of new drugs intended for treatment of orphan diseases. The number of issued orphan designations in the USA and the EU grows from year to year (Fig. 1).Since 2003, as it can be seen from Fig. 1, the number of issued orphan designations has substantional growth. The main reason for this situation was the introduction of EMA regulation for orphan drugs in 2000 and the provided possibility for submitting a joint application for receiving an orphan designation by both regulatory agencies (FDA and EMA) at the same time [8].



2.1 Regulation for orphan drugs in USA, FDA regulation

The FDA orphan drugs regulation is based on three laws that apply to orphan drugs [11].

The first regulation for orphan drugs is the Orphan drug act,for the first time presented in the far1983.This act seeks to protect an orphan drug which has to be produced and marketed by some pharmaceutical company. It includes not only drugs which are intended for treatment of diseases that affects less than 200.000 people in the USA, but also drugs for any other diseases that affect more than 200.000 people in USA and for which there is no reasonable expectation that the cost of developing and making available these drugs in the USA would be recovered from it sales. On one hand, this act assumes that the drugs intended for treatment ofrare diseases need patent protection and on the other hand, this act left the possibility producers of medicines which are not intended for treatment of rare diseases also to obtain patent protection for their final products. The practical experience of using this regulation showsthat it is focused on research and development of new drugs intended for treatment of rare diseases. The loudest critics and opponents of this legislation emphasize that according this act, some drugs could ensure reliable profit of 1 billion US dollars annually, with remark that the same drug will be developed and marketed without receivingany orphandrug designation and without using any incentives connected to this orphan drug designation. The biggest abuse strategy of this legislation, used by the pharmaceutical company in practice, is the strategyknown as a "salami slicing" strategy. According to this strategy, the pharmaceuticalcompany first starts with a design of clinical trials that involve small portion of patientsin order to receivean orphan drug designation and to use all incentives connected with this designation.Subsequently, the company starts new clinical trials that involve a bigger portion of patients and reference these new data the drug would be available for use by larger portion of patients [11].

The second legislation is the legislation for protection from generic competitors.Referenceto this legislation, after receiving an orphan designation, FDA could not give an approval to some other drug which is the same with already approved orphan drug, but produced by the other pharmaceutical company for the period from five to seven years. The main purpose of this legislation is to discourage the idea for development of non-patent drugs. Considering the fact that generic drug may appear on the market only in case when the company producer of this generic drug submits their own data from their own clinical trials, the scope of full drug protection provided by this legislation is less than the protection provided through the Orphan Drug Act.This kind of exception was not allowed by the Orphan Drug Act.The legislation gives theability for free use of the final information from other successfully conducted and completed clinical trials as a further relief to generic company where, besides the cost of the clinical trials, the risk of whether the study will be successful or notarises as a problem [11].

The third legislation which is a part of FDA regulation for orphan drugs isHatch-Waxman Act.According to this legislation, the generic company asa producer of generic drug which challenge the original drug under patent protection, could receive a 180 days periodof exclusivity. During theperiod of exclusivity no otherproducer could put on the market thesamegeneric drug.According to this act, the authorised generic company may charge more than thereal costs and it is allowed to make anextra profit and to receive other benefitswhile it challenges the original drug under patent protection. Hatch-Waxman actmay tolerate various agreements concluded between the company producer of the original drug and company producer of the generic drug, but it should be noted that only agreements which are focused to the time ofentering thegeneric

drug on the market are allowed.Agreements which apply of exchange of funds or any other kind of compensation are not permited [11].

In daily practice, Orphan Drug Act reflects a dual concern. One concern of this legislation refers to the fact that only few companies will be interested to start business activities, if the first step in this business process is high-costly regulatory approvals. Another concern of this legislation relates to the fact that the success of the first companies in the business process will be the main reason for attempting of other companies in the same business.Opposed of the Orphan Drug Act, Hatch-Waxman act reflects the concern when the first step in this business process is expensive litigation.Despite a number of shortcomings or contradictions, the application of these legislations, generally is characterized with:

- anticipating of all possible agreements which are concluded between the parties whose interests are affectedwith these legal decisions. As an example of this is the fact that Hatch-Waxman act may tolerate a various agreements concluded between the company producer of original drug andcompany producer of generic drug,as mentioned above;
- able to detect all possible company's activities which are aimed for providing legal exclusivity, but where noone of these corporate activities should not prevent other companies to get the opportunity for exclusivity;
- caution delineation of the scope of exclusivity;generally, these legislations prohibits the possibility ofauthorized products, but in the absence of any written statements, courts in practice often decide in favor of theinventor and the patent holder;
- highlighting the fact that the term exclusivity in itself involves identifying of events and preconditions as acondition for the status of exclusivity and the same events and preconditions should be clearly defined and specified.

2.2 Regulation for orphan drugs in EU, EMA regulation

At the European Union level, the first known regulations related to the definition of rules for obtaining orphan drug designation is EC Regulation 141/200 (Orphan Regulation), adopted in December 1999. Today, the total legislation for orphan drugs in EU is covered by six regulations and two additionalguidelines for implementation of the regulations [12].According to EMA regulations, a drug which isintendedfor treatment of rare disease or condition which affects not more than 5 in10.000 people in the EU is definedas an orphan drug.
The medicinal product would be designated as an orphan medicinal product in EU if its sponsor could demonstrate [13]:

- that it is intended for diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in10.000 people in the Community when the application is made;or
- that it is 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;and
- that there exists 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, that the medicinal product will be of significant benefit to those affected by that condition.

Reference to EMA regulations and EMA rules, the company which is producer of a potential orphan drug, first has to submit an application for evaluation to the EMA's Committee for orphan medicinal products (COMP) [14].The task of this Committee are:

- to examine any application for the designation of a medicinal product as an orphan medicinal product which is submitted to it in accordance with European regulation for orphan drugs;
- to advise the European Commission on the establishment and development of a policy on orphan medicinal products for the European Union;
- to assist the European Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;
- toassist the European Commission in drawing up detailed guidelines.

After reviewing thesubmitted application,COMPgives its opinion to the European Commission whetherthis drug meets the requirements for receiving an orphan designation. Based on this opinion, the European Commission may give or not an orphan designation for some drug. Reference this rule it could concluded that the COMP has the right to decide and the European Commission has a right for assigning a drug as an orphan drug.

For all designated orphan medicines centralized procedure for marketing authorizationis obligatory.It covers all European Economic Areas countries (EU countries plus Iceland, Liechtenstein and Norway).

III. DISCUSSION

The comparison of the regulatory requirements relating to orphan drugs between FDA and EMA shows that in the USA they are defined by three laws that apply to orphan drugs:Orphan Drug Act, Protection from generic competition and Hatch-Waxman Act. In the EU these regulatory requirements are defined by six regulations and two additional guidelines with instructions for their individual implementation.According to the defined regulatory requirements,if a drug is designated as an orphan drug, the company producer of this medicine could use a variety of incentives defined by FDA and EMA, for USA and EU, respectively.

The pharmaceutical company as a producer of the drug with orphan designation issued by FDA, receives [11]:

-protocol assistance;
- shortened procedure of registration;
- market exclusivity for period of five to seven years;
- the company owner of orphan designation receive a tax incentives;
- exemption from payment of certain fees and grants.

For example, the company could use an orphan creditfrom themoment when its drugreceives an orphandesignation until it gets permission by the FDA for the use by patients. With this type of credit could be cover the costs which companymay have for additional tests and research, which would be set by the FDA.

The pharmaceutical company as a producer of the drug with orphan designation issued by EMA, receives [15]:

-protocol assistance;
- access to centralized approval procedure for marketing authorization;
- period of ten years market exclusivity, with possibility of additional two yearsmarket exclusivity for drugs that have valid and approved pediatric researchplan (pediatric investigation plan);
- compensationfor micro, small and medium-sized companies;
- exemption from payment of certain fees;
- grantsandadditional national incentives in some EU member states.

Protocol assistance is a form of scientific advice provided by the FDA and the EMA, specifically for orphan medicines. This allows sponsors to get answers to their questions on the types of studies needed to demonstrate the medicine's quality, benefits and risks, and information on the significant benefit of the medicine. These two regulatory authorities have initiated a program, known as a "General Principles" program to provide Parallel Scientific Advice. The goal of this program is to provide a mechanism for EMA and FDA assessors and sponsors to exchange their views on scientific issues during the development phase of new medicinal products. The expected advantages from such interactions are increased dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, a deeper understanding of the bases of regulatory decisions and the opportunity to optimize product development and to avoid unnecessary testing replication or important breakthrough drugs or important safety issues in the following areas which have been identified as clusters of interest between the agencies: oncology, vaccines, orphan drugs, drugs in pediatric population, nanotechnologies, advanced therapies, pharmacoeconomics and blood products. Parallel scientific advice procedures are conducted under the auspices of the confidentiality arrangement between the EMA and FDA. These two regulatory agencies agree that making this "General Principles" statement public on the website of both agencies would make the program procedures and goals more transparent and would give an answer to many questions about the program that may exist in the general public. Each agency posted this statement on its website in accordance with its own procedures for posting such documents.Protocol assistancecould be asked in any time, started at the moment when company decide to submit application for receiving orphan designation until the moment of submitting of the application.There is no restriction for the sponsor on the number of times of the request protocol assistance.

The centralized procedure for marketing authorizationin the EU is obligatory in the case of orphan drugs.At the EU level, EMA clearly defines the criteria by which some pharmaceutical company may be defined as a micro, small or medium-sized company, but generally companies must be established in the European Economic Area (EEA), employ less than 250 employees and have an annual turnover of not more than 50 million euros or an annual balanced-sheet total of not more than 43 million euros. According this, there are different types of incentives which the company may receive after obtaining an orphan designation [16].

Both regulatory authorities, stimulate the process of parallel application by advising the companies to use the "common orphan application form" in order to obtain orphan designationin both in USA and EU.EMA also has special arrangements for parallel application with Japan, with their Ministry of Health, Labor and Welfare.

IV. CONCLUSIONS

The detailedcomparativeoverview of the FDA and EMA regulatory requirements, respectively for USA and EU, emphasizesseveral similarities and differences between the incentives that these two regulatory bodies give to the companies that produce orphan drugs.

Both regulatory bodies givesshortenedmarketing authorizationprocedure, allow exception from payment of certain fees, provide protocol assistance and stimulate processes of a parallel application for orphan designation. The differences could be seen in the part of market exclusivity, tax incentives and sources of grants.Market exclusivity, according to FDA's rules is limited to seven years, unlike of EMA where on the first assigned ten years, there is possibility for additional two years, only for drugs with valid and approved pediatric research plan (pediatric investigation plan).The tax incentives at the level of the USA are defined by the FDA and apply to all countries members of the United States.In the EU there are general tax incentives defined by the EMA for all EU member states, butthere is the possibility for additional national tax incentives in cases where some member state of the EU considers that this decision is necessary for certain orphan drug.

Both regulatory authorities provide grants to pharmaceutical companies, but the difference is in the source of these means. In the FDA these means are provided by the FDA orphan product grant program as a part of FDA. Contrary to FDA, EMA does not provide any grants from its own budget. The companies in EU level, could provide grants through European commission and other sources such asHorizont 2020, the EU Framework Program for Research and Innovation;E-Rare, a transnational project for research programs on rare diseases and International Rare Diseases Consortium (IRDIRC).

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