ARTICLES

ORPHAN DRUGS FOR THE TREATMENT OF RARE DISEASES. A COMPARATIVE PUBLIC LAW PERSPECTIVE

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Abstract

This article aims to analyse the regulatory framework of the orphan drugs for the treatment of rare diseases. After defining the concepts of "orphan drug" and "rare disease" and reviewing the U.S. and European regulatory regimes, the essay examines the Italian legislation and, in particular, the balance of the current distribution of expenditure between public bodies and private economic operators. The article reaches the conclusion that current Italian framework represents a best practice: it allows the most appropriate constitutional balance between public interest, private economic operators interest and right to health of individuals.

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1. The concepts of "rare disease" and "orphan drug". The distinction between orphan drug and innovative drug

The evocative name of American origin "orphan drug" is now in common use throughout the world. The term "orphan drug" refers to medicines for the treatment of rare diseases and conditions affecting a limited percentage of individuals[1]. The high research, development, and commercialisation costs for these drugs is uneconomical[2] for pharmaceutical companies due to the small number of potential paying patients; so, being unable to "survive alone" in a competitive environment they need to be "adopted" by public health system[3].

Legislation must therefore envisage a number of means to allow coverage for investment in research and development by private companies, including forms of financial or fiscal incentives, the distribution of costs between the State and private operators in the sector, and temporally limited exclusive drug commercialisation rights. The scenario is therefore one in which the market alone is unable to yield positive results, entailing substantial public intervention in terms of planning and management to bring about an adequate balance that will allow patients suffering from rare conditions to hope in a cure, and

[1] See, *ex multis*, S. Panunzio, G. Recchia (eds.), *Malattie rare: la ricerca tra etica e diritto* (2007).

[2] In addition to the term "orphan drugs", the expression "uneconomic drugs" is also used.

[3] On the positive effects of competition in the pharmaceutical market, see, *ex multis*, L. Arnaudo, G. Pitruzzella, *La cura della concorrenza. L'industria farmaceutica tra diritti e profitti* (2019).

pharmaceutical companies to meet the costs of research and development.

Consequently, European Union legislation has established appropriate multi-level administrative procedures for the designation of a medicinal product as an "orphan medicinal product" and to authorise placing it on the market (marketing authorisation), which has led to a specific and favourable regime for companies that produce medicines of this kind[4].

A condition is considered "rare" when its prevalence (i.e. the number of cases diagnosed at a precise moment in time for a given population) does not exceed a certain conventionally fixed threshold. In Europe, the current rules on orphan medicinal products state that a "[c]ondition with a prevalence of not more than five affected persons per 10 thousand is generally regarded as the appropriate threshold"[5]. Community action programme runs along the same lines, according to which a rare disease is one which does not exceed the threshold of 0.05% of the population, or approximately one case per two thousand inhabitants or five cases per ten thousand individuals[6]. More recently, the rules governing clinical trials on medicinal products for human use have established that "severe, debilitating and often life-threatening diseases affecting no more than one person in 50,000 in the Union"[7] are to be regarded as rare. In other parts of the world the parameters are different, although quite close to those established for Europe: in the United States, conditions affecting less than two hundred thousand people are considered rare (approximately 0.08% of the population; around 7.5 cases per ten thousand individuals); in Japan, all conditions that do not exceed fifty thousand cases (around four cases per ten thousand inhabitants);

[4] Under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, on orphan medicinal products, point 1 of the preamble states that "some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are therefore called 'orphan'".

[5] See Regulation (EC) No. 141/2000, point 5 of the Introduction.

[6] Programme of Community action on rare diseases 1999-2003.

[7] See Regulation (EU) No. 536/2014, point 9 of the Preamble.

in Australia, the parameter is narrower, as conditions affecting 1.2 people per ten thousand are considered rare.

Despite the rarity of these conditions, they affect a large proportion of the world population. In the United States, between twenty and twenty-five million inhabitants suffer from rare diseases; in Europe, 7% of the population, or just under thirty-five million inhabitants, suffer from such conditions; in Italy, estimated figures of over two million affected inhabitants have been returned. According to World Health Organization (WHO) statistics, rare diseases account for 10% of known conditions and are extremely diversified: it is estimated that the number of such diseases known and diagnosed falls between the seven- and eight-thousand mark[8]. In addition to being very difficult to diagnose, about 98% of rare diseases are not currently without pharmaceutical treatment of proven effectiveness (only about one-hundred-and fifty diseases are, at present, curable). This figure has serious repercussions: almost 30% of children suffering from a rare condition die before the age of five.

Under current European legislation, a drug for the treatment of a rare disease is classified as "orphan" "if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or 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, 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 (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been

[8] Internationally, there are at least three major lists of rare diseases: the National Organization of Rare Disease (NORD), the Office of Rare Disease, and Orphanet. Upon recommendation of the Italian Ministry of Health, with Ministerial Decree No. 279/2001 (Regulation establishing the national network of rare diseases and exemption from participation in the cost of related health services), the *Istituto Superiore della Sanità* drew up a list of rare diseases for the purposes of exemption from contribution. To exemplify the vastness and heterogeneity of the conditions, suffice it to mention glioma, multiple myeloma, cystic fibrosis, spinal muscular atrophy, and familial hypercholesterolemia, in addition to some better-known diseases, such as AIDS.

authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition"[9].

A number of points can be inferred from this definition: a) the product of a piece of scientific research must be submitted to an administrative procedure in order to obtain specific legal recognition; it is therefore subject to on an authoritative provision with a view to verifying whether it meets a series of requirements established in the regulatory framework[10]; b) the drug has a sponsor[11] (often a pharmaceutical company) that submits the application for qualification: it follows that the procedure is at the request of one party and, therefore, the input comes from a private initiative; c) the drug may be defined as "orphan" under any one of the following sets of circumstances: the purpose of the drug (it must be used to diagnose the condition, as a prophylaxis, or a treatment), the severity of the disease (which must involve a threat to life or chronic debilitation), statistical data concerning the rarity of the disease at a given time (the disease must affect fewer than five people in ten thousand at the time the application is submitted), a need for the drug due to a lack of other effective treatments or the particularly beneficial results that the new drug can bring to patients; the second set is open, however, as it is not limited by statistical data; given the seriousness of the condition and the necessity of the medicine, it is linked to economic factors (the uneconomic nature of commercialisation in the absence of incentives)[12].

Italian law adds nothing new to the European definition of 'orphan drug', merely referring to Regulation (EC) No. 141/2000

[9] See Article 3 of Regulation (EC) No. 141/2000.

[10] See the next section about more on this.

[11] Regulation (EC) No. 141/2000 identifies the applicant as a "sponsor", which it defines as "a legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product".

[12] See also Commission Communication on the application of Articles 3, 5 and 7 of Regulation (EC) No. 141/2000 on orphan medicinal products. Commission Regulation (EC) No. 847/2000, establishing the provisions for implementing the criteria for defining a medicinal product as "orphan", together with the definition of "similar" and "clinical superiority", sets out more detailed criteria to enable applicants to prove that they meet the requirements for orphan medicines.

and its requirements[13]. The notion of orphan drug must be clearly distinguished from that of innovative drug, with which it is sometimes mistakenly confused. While the first concerns a rare condition (with all this entails in terms of the disadvantageous investment), "innovative" drugs relate to more common diseases whose prevalence exceeds the normal thresholds of distribution[14]. Once the degree of innovation has been assessed by the competent administrative authorities (in Italy by the Italian Medicines Agency, the *AIFA*), innovative drugs benefit from incentives to encourage pharmaceutical companies to invest in scientific innovation and improved treatments. Innovative drugs are identified as such using three parameters: the necessity for the treatment, its added therapeutic value, and the quality of evidence or the robustness of clinical studies. The need for treatment is conditioned by the existence of therapies for a given condition and indicates to what extent the new treatment can provide advanced responses to existing therapeutic needs; the added therapeutic value is determined by the extent of the clinical benefit, if any, that the new drug can bring compared with the alternatives available; the quality of the evidence is shown by the scientific validity of the elements produced to support the innovation. In conclusion, innovative drugs too can benefit from incentives due to the degree of scientific progress that the product can contribute to achieving, but – once on the market – they are able to support themselves through sale to a large number of patients, which is not the case of orphan drugs.

In order to examine the numerous legal issues surrounding orphan drugs, after focusing on U.S. regulation and other comparisons, it may be appropriate to take the analysis of organisational structure and procedural dynamics as a starting point for obtaining the status of orphan drugs and their commercialisation in Europe and Italy. There follows an examination of how the price of an orphan drug is established and how the exclusive rights normally enjoyed by companies commercialising the orphan drug work. The second half of the paper focuses on the topic of greatest interest in relation to orphan

[13] See Article 15 (8) letters i) and i-bis) of Decree Law No. 95/2012, converted into Law No. 135/2012.

[14] F. Anastasi, *La tutela della salute e le esigenze della concorrenza: un difficile bilanciamento per i farmaci innovativi*, in 2 Amministrazione in cammino 1 (2017).

drugs, namely the methods of distributing the costs envisaged by the various legal systems, with particular reference to Italy.

We use the European and Italian rules as a point of reference, aware that elements of global law and other important disciplines in the sector in other countries need also to be considered[15] – starting from the oldest: the 1983 Orphan Drug Act (ODA)[16], leading to amendments to the Federal Food, Drug, and Cosmetic Act – which we will use as a measure of comparison with the former.

Ultimately, this paper deals with two fundamental rights of the person. The first concerns the protection of the health of persons suffering from rare conditions. Diseconomies arising in this area must not be allowed to weaken the constitutionally protected right to health of patients suffering from such illnesses, meaning the right to health treatments of proven effectiveness and also to hope in the development of new forms of treatment as a result of the progress of pharmacological research. For these reasons, the indisputable need to ensure that people suffering from rare conditions receive the same treatment and healing opportunities as any other patient is the basis of special regulations for this type of drug, where the dynamics of the economy are largely replaced by corrective measures of an authoritative nature.

The second fundamental right, related to the first, concerns more generally the right of access to a drug and the circumstance that the major companies operating in the sector across the globe may, in order to be able to cover the costs of research and development in the absence of a sufficient number of beneficiaries, legally enjoy monopoly status, with sometimes serious repercussions in terms of costs for patients and/or the community (in some legal systems, even to the point of barring treatment, effectively condemning patients with rare conditions to death). It is necessary to understand what degree of profit margin companies need to be guaranteed under these circumstances when

[15] With regard to the European (and global) regulation of pharmaceuticals, see, among others, A. Spina, *The Regulation of Pharmaceuticals Beyond the State: Global administrative law and global administrative law*, in E. Chiti, B.G. Mattarella (eds.), *Global Administrative Law and EU Administrative Law. Reports, Legal Questions and Comparison* (2011), 249 ff.

[16] 97th Congress, Public Law 97-414, 4 January 1983 (H.R. 5238).

they invest capital in finding a cure for rare diseases and what dysfunctions are to be avoided in order to prevent excessive economic benefits for the pharmaceutical companies and costs that are too high for patients and their families to bare. The ideal starting point for an analysis of the administrative procedures for defining and placing orphan drugs on the market is the legal system of the United States, which was the first to introduce rules on orphan drugs.

2. U.S. regulation

The United States was the first country to introduce regulatory measures to encourage investment by pharmaceutical companies in unprofitable fields[17]. This means, for example, providing subsidies and tax incentives or guaranteeing exclusive distribution of a drug for a certain number of years, thereby ensuring such companies an adequate profit margin.

[17] See, *ex multis*, C.A. Thomas, *Re-Assessing the Orphan Drug Act*, in 12 J.L. & Soc. Probs. 413 (1990); C.H. Asbury, *The Orphan Drug Act: The First 7 Years*, in 265 (7) JAMA 893 (1990); S.E. Lawton, *Controversy Under the Orphan Drug Act: Is Resolution on the Way?*, in 327 (46) Food Drug Cosm. L.J. 327 (1991); J.J. Flynn, *The Orphan Drug Act: an Unconstitutional Exercise of the Patent Power*, in Utah L. Rev. 389 (1992); A.M. Garber, *Benefits Versus Profits: Has the Orphan Drug Act Gone Too Far?* (1994), 88 ff.; M. Thamer, N. Brennan, R. Semansky, A *Cross-National Comparison of Orphan Drug Policies: Implications for the U.S. Orphan Drug Act*, in 23 J. Health Pol., Pol'y & L. 265 (1998); G.A. Pulsinelli, *The Orphan Drug Act: What's Right with It, Santa Clara Computer & High Tech*, in 12 L.J. 299 (1999); A.K. Rai, *Pharmacogenetic Interventions, Orphan Drugs, and Distributive Justice: The Role of Cost-Benefit Analysis*, in 19 Soc. Phil. & Pol'y 246 (2002); T. Maeder, *The Orphan Drug Backlash*, in 19 Sci. Am. 80 (2003); D. Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, in 15 Am. J.L. & Med. 365 (2005); R. Rogoyski, *The Orphan Drug Act and the Myth of the Exclusivity Incentive*, in 32 Colum. Sci. & Tech. L. Rev. 1 (2006); M. Abramowicz, *Orphan Business Models: Toward a New Form of Intellectual Property*, 12 Har. L. Review 1363, 1421 (2011); M. Herder, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the USA and in Canada*, in 12 Jour. L. & Biosc. 158, 166 (2016); J.B. Bannister, *Regulating Rare Disease: Safely Facilitating Access to Orphan Drugs*, in Fordham L. Rev. 1889 (2018).

2.1. The regulatory framework and organisational/functional solutions

The ODA assumes that there is a public interest in the development of orphan drugs and consequently in providing public incentives following the failure of the market[18], granting drugs designated as "orphan" special legal status.

To this end, it provides that, in the event of approval, certification or licensing[19] of the medicinal product by the Food and Drug Administration (hereinafter FDA) for the treatment of rare diseases, the Secretary of State for Health and Social Welfare will grant a seven-year industrial patent to the researcher or pharmaceutical company that submitted the application for accreditation of the medicinal product.

In addition, the Secretary grants funding to cover the costs of qualified clinical trials and the development of medical devices and medical foods[20]. This legislation also establishes a number of tax incentives.

Lastly, the ODA provides for the establishment within, the Department of Health and Human Services, of an Orphan

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[18] "The Congress finds that (…): (1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States; (2) adequate drugs for many of such diseases and conditions have not been developed; (3) drugs for these diseases and conditions are commonly referred to as 'orphan drugs'; (4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss; (5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and (6) it is in the public interest to provide such changes and incentives for the development of orphan drugs".

[19] These are the three drug accreditation scenarios provided for in Sections 505 and 507 of the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act.

[20] "The term 'medical food' means a food which is formulated to be consumed or administered entirely under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation".

Products Board[21] tasked with promoting, assessing, consulting and sector budgeting.

[21] "(a) There is established in the Department of Health and Human Services a board for the development of drugs (including Biologics) and devices (including diagnostic products) for rare diseases or conditions to be known as the Orphan Products Board. The Board shall be comprised of the Assistant Secretary for Health of the Department of Health and Human Services and representatives, selected by the Secretary, of the Food and Drug Administration, the National Institutes Health, the Centers for Disease Control and, any other Federal department or agency which the Secretary determines has activities relating to drugs and devices for rare diseases or conditions. The Assistant Secretary for Health shall chair the Board; (b) the function of the Board shall be to promote the development of drugs and devices for rare diseases or conditions and the coordination among Federal, other public, and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions; c) in the case of drugs for rare diseases or conditions the Board shall (…) (1) evaluate (…) (A) the effect of subchapter B of the Federal Food, Drug, and Cosmetic Act on the development of such drugs, and (B) the implementation of such subchapter; (2) evaluate the activities of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration for the development of drugs for such diseases or conditions, (3) assure appropriate coordination among the Food and Drug Administration, the National Institutes of Health, the Alcohol, Drug Abuse, and Mental Health Administration, and the Centers for Disease Control in the carrying out of their respective function relating to the development of drugs for such diseases or conditions to assure that the activities of each agency are complementary, (4) assure appropriate coordination among all interested Federal agencies, manufacturers, and organizations representing patients, in their activities relating to such drugs, (5) with the consent of the sponsor of a drug for a rare disease or condition exempt under section 505(i) of the Federal Food, Drug, and Cosmetic Act or regulations issued under such section, inform physicians and the public respecting the availability of such drug for such disease or condition and inform physicians and the public respecting the availability of drugs approved under section 505(c) of such Act or licensed under section 351 of this Act for rare diseases or conditions, (6) seek business entities and others to undertake the sponsorship of drugs for rare diseases or conditions, seek investigators to facilitate the development of such drugs, and seek business entities to participate in the distribution of such drugs, and (7) reorganize the efforts of public and private entities and individuals in seeking the development of drugs for rare diseases or conditions and in developing such drugs; (d) the Board shall consult with interested persons respecting the activities of the Board under this section and as part of such consultation shall provide the opportunity for the submission of oral views; (e) the Board shall submit to the Committee on Labor and Human Resources of the Senate and the Committee on Energy and Commerce of the House of Representatives an annual report (…) (1) identifying the drugs which

These forms of incentives have led to significant development in the orphan drugs sector. As early as 1993, the Office of Rare Diseases Research (ORDR) was informally established as part of the office of the Director of the National Institutes of Health (NIH), the federal agency for health research. In the light of its rapid development, Congress passed the Rare Diseases Act (RDA) in 2002, which gave the ORDR legal recognition. The ORDR is headed by a Director (appointed by the Director of the NIH)[22].

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have been designated under section 526 of the Federal Food, Drug, and Cosmetic Act for a rare disease or condition, (2) describing the activities of the Board, and (3) containing the results of the evaluations carried out by the Board. The Director of the National Institutes of Health and the Administrator of the Alcohol, Drug Abuse, and Mental Health Administration shall submit to the Board for inclusion in the annual report a report on the rare disease and condition research activities of the Institutes of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration; the Secretary of the Treasury shall submit to the Board for inclusion in the annual report a report on the use of the credit against tax provided by section 44H of the Internal Revenue Code of 1954; and the Secretary of Health and Human Services shall submit to the Board for inclusion in the annual report a report on the program of assistance under section 5 of the Orphan Drug Act for the development of drugs for rare diseases and conditions. Each annual report shall be submitted by June 1 of each year for the preceding calendar year".

[22] More specifically, the tasks of the Director of the ORDR are as follows: " (1) IN GENERAL. - The Director of the Office shall carry out the following: (A) The Director shall recommend an agenda for conducting and supporting research on rare diseases through the national research institutes and centers. The agenda shall provide for a broad range of research and education activities, including scientific workshops and symposia to identify research opportunities for rare diseases. (B) The Director shall, with respect to rare diseases, promote coordination and cooperation among the national research institutes and centers and entities whose research is supported by such institutes. (C) The Director, in collaboration with the directors of the other relevant institutes and centers of the National Institutes of Health, may enter into cooperative agreements with and make grants for regional centers of excellence on rare diseases in accordance with section 404G. (D) The Director shall promote the sufficient allocation of the resources of the National Institutes of Health for conducting and supporting research on rare diseases. (E) The Director shall promote and encourage the establishment of a centralized clearinghouse for rare and genetic disease information that will provide understandable information about these diseases to the public, medical professionals, patients and families. Reports. (F) The Director shall biennially prepare a report that describes the research and education activities on rare diseases being conducted or supported through the national research institute and centers, and that

Thanks to the RDA, in addition to providing the ORDR with specific legal status, funding has been substantially increased to foster the development of diagnosis and treatment for patients with rare diseases.

Lastly, in 2012, again as part of the NIH scenario, the ORDR became a division of the National Center for Advancing Translational Sciences (NCATS), with the task, among other things, of overseeing the Rare Diseases Clinical Research Network and the Genetic and Rare Diseases Information Center.

Essentially, the ORDR is therefore tasked with planning research on rare diseases, promoting and supporting research, and training researchers in cooperation with other health institutions, promoting a clinical research network for rare diseases, managing and encouraging research cooperation on rare diseases. It will also boost scientific opportunities and help to increase international cooperation, promoting an extensive programme of scientific meetings, providing information concerning rare diseases, and will compile an annual report for Congress on the rare disease activities of the NIH.

The other front relating to orphan drugs is that within the FDA whose purpose is to perform all the activity that precedes – and leads up to – marketing authorisation of the drug. The Office of Orphan Products Development (the OOPD) was established there in 1983. Its purpose is to assess and develop products (medicines, biological products, equipment, medial foods) that may be promising in terms of diagnosing and treating rare diseases. The task of the OOPD is therefore to promote the availability of safe and effective products for the treatment of rare diseases by qualifying them as "orphans". This status allows the drug, at any stage of development (research, development, and commercialisation), to benefit from incentives to implement them

identifies particular projects or types of projects that should in the future be conducted or supported by the national research institutes and centers or other entities in the field of research on rare diseases. Reports. (G) The Director shall prepare the NIH Director's annual report to Congress on rare disease research conducted by or supported through the national research institutes and centers. (2) Principal advisor regarding orphan diseases. - With respect to rare diseases, the Director shall serve as the principal advisor to the Director of NIH and shall provide advice to other relevant agencies. The Director shall provide liaison with national and international patient, health and scientific organizations concerned with rare diseases".

until marketing authorisation is granted. In addition to collaborating with research and medical institutions, professional organisations, universities, government agencies, pharmaceutical companies, patients' associations for persons with rare diseases, on receiving a special request from the sponsor, the OOPD assesses the scientific and clinical results presented with a view to the possible qualification of the product in terms of effectiveness for the treatment of rare diseases and the advancement of scientific knowledge in the field, also creating the possibility of providing incentives for the development of this product. Drugs and biological products that are considered promising for the diagnosis and treatment of rare diseases are included in the Orphan Drug Designation Program; devices that pass OOPD screening are included in the Humanitarian Use Device (HUD) Program. If a drug or biological product is approved for the treatment of rare paediatric diseases, it will come under the Rare Pediatric Disease Priority Review Voucher Program. This means that a bonus is made available that can be used to obtain priority investigation for later marketing authorisation concerning a different product. This is a very interesting measure because of the originality of the reward system, but also due to the degree of importance that the legal system gives the treatment of diseases affecting children. Lastly, the OOPD runs various subsidy programmes for external subjects: the Orphan Products Grants Program allocates funds for clinical research aiming to demonstrate product safety and effectiveness; the Pediatric Device Consortia (PDC) Grants Program provides funding for the development of non-profit consortia with a view to developing pediatric medical devices; the Orphan Products Natural History Grants Program finances studies to encourage the development of knowledge about rare diseases through methods, paradigms, and indicators typical of natural history.

Drugs are classified as "orphan" upon successful completion of the procedure, and a seven-year patent is granted to the sponsor who submitted the application. In addition to data relating to the promoter and the drug (the name and address of the promoter, the name and address of the manufacturer, the international common name and trade name of the drug), the application must contain a description of the condition for which the use of the drug is to be used and the conditions of use, as well

as the number and main characteristics of the population likely to be treated. Furthermore, a description of the drug and its risk/benefit ratio or a summary of the main pre-clinical and clinical data on the use of the product, as well as basic documentation must be provided. Lastly, an estimate of the development and distribution costs and an assessment of the sales potential in the United States, confirming the lack of profitability of placing the product on the market in specific cases, must be submitted. The FDA must respond within a maximum of sixty days after receiving the request. Information regarding the "orphan" status awarded is published in the Federal Register. Achieving orphan drug classification and marketing authorisation are necessary steps in placing an orphan drug on the market.

If the drug is apparently identical to a product already approved for the same condition, the applicant company must be able to demonstrate the clinical superiority of its own drug, which will then be considered as a new active substance. The effectiveness of the drug must be demonstrated in terms of the prevention, diagnosis, or treatment of a rare disease. The products of more than one pharmaceutical company may be classified as orphan drugs for the same ailment, but the period of market exclusivity is granted to the sponsor who applies for commercialisation first. Competitors have the right to market drugs for other ailments during the period of exclusivity.

Obtaining orphan drug status gives a pharmaceutical company market exclusivity for seven years after the drug is placed on the market, plus the following benefits for product development: a 50% tax credit on the cost of clinical trials conducted in the United States; the preparation of written recommendations by the FDA regarding clinical and pre-clinical studies that must be completed in order to register the new drug, and an accelerated FDA registration procedure.

In certain cases of particular urgency, orphan drugs may be made available to patients before they are placed on the market. The compassionate use of a Treatment Investigational New Drug (T-IND) may be possible when the following conditions are met concurrently: the drug must be intended for the treatment of a serious or life-threatening condition; no alternative drug or treatment is available; the product must already be subject to clinical trials and must be in an active phase of marketing

authorisation approval. T-INDs are granted for a limited period of time.

2.2. Possible misapplications in the U.S. scenario

As mentioned above, in United States, the orphan drugs sector has experienced a surprising and over-rapid development, proving to be an important market area for pharmaceutical companies[23]: over recent years, shares in the main companies in the sector have reached a rating of 25%, and the gains on sales of orphan drugs have been very high. This development has also given rise to sensitive application issues. The main problems that have come to light are outlined below.

For some orphan drugs, problems similar to those affecting non-orphan drugs have been identified: for example, it has been found that the selling price is disproportionate to the costs of the drug's research, development, and production (the case of hepatitis C drugs is sadly a well-known example). But there are also specific dysfunctions deriving from orphan drug classification.

The first of these is companies seeking orphan drug status in order to benefit from subsidies for research and development, tax and regulatory incentives, as well as patent benefits, only to apply later for permission to market the drug for the treatment of non-rare conditions. An emblematic example is a drug that was granted orphan status for the treatment of familial hypercholesterolemia, and the company enjoyed a significant number of economic benefits for development, testing, and bringing to the market. After some time, the company applied to the FDA for authorisation to market the product for the reduction of cholesterol levels in all diabetics, making enormous profits. EPO and the growth hormone (very well known for their use in

[23] See, *ex multis*, A.S. Kesselheim, *An empirical review of major legislation affecting drug development: past experiences, effects, and unintended consequences*, in 11 Milbank Q. 450, 502 (2011); U. Reinhardt, in *Probing our moral values in health care: the pricing of speciality drugs,* 314 JAMA 381 (2015); N. Bagley, B. Berger, A. Chandra, C. Garthwaite, A.D. Stern, *The Orphan Drug Act at 35: Observations and an Outlook for the Twenty-First Century*, in J. Lerner, S. Stern (eds.), *Innovation Policy and the Economy* (Volume 19) (2018), 97, 137; J. Sheridan, *Billion Dollar Orphans: Tension Between the Legal Intent and Social Purpose of the Orphan Drug Act*, 112 Tex. A&M L. Rev. 731 (2019).

doping in sport) followed the same path. The growth hormone is used to treat dwarfism in children: there are 10,000 children in the USA suffering from this condition, but the drug, which has very high prices due to the exclusivity regime, has brought an income of 120 million dollars per year.

It is indisputable that the pharmaceutical companies' earnings from orphan drugs are on the steady increase. Suffice it to recall the following data: while, in the past, the so-called blockbuster drugs (those capable of generating profits in excess of at least one billion dollars a year) were intended to treat traditional diseases, with a large pool of patients, in the 2015 ranking for the ten best-selling drugs in the world, seven were orphan drugs (the second best-selling drug is Humira which has a guaranteed revenue of more than fourteen billion dollars, while the other six all exceed revenues of five billion dollars). In the United States alone, in 2015, more than one-hundred-and-seven billion dollars were spent on the purchase of orphan drugs, and further growth in market share is forecast. These substantial earnings are mainly due to the cost of orphan drugs, on average twenty times higher than traditional drugs. But also – and especially – in addition to the abuse mentioned above, the original classification as "orphan" is later updated to include other "traditional" therapeutic uses: around 15% of the drugs classified as orphan are later recommended for other conditions; in Europe, eleven of the twenty best-selling orphan drugs have been designated for cancer treatment. In addition, orphan drugs can easily be used in off-label settings, regardless of the initial strict limitations, with all the ensuing benefits.

A second case of misuse of the special arrangements is the ability to enjoy exclusive market of an orphan drug for seven years, thus avoiding competition from other companies and keeping prices extremely high. In the case of two companies working simultaneously on the research and development of an orphan drug: the one that arrives first takes all, and the other company, despite all the expenses it has had to stand, will be out of the game for at least seven years, unless it can prove that its drug has a greater or, at least, distinct efficacy compared with the first one. In the political debate in Congress, several attempts have been made to remove the monopolistic system of rights. However, these attempts have all failed, and what is most striking is that, in

addition to the lobbying opposition of the companies involved, these initiatives have also had to face the opposition of associations of patients suffering from rare diseases, fearful of the introduction of measures that could jeopardise a system that has, all things considered, produced useful results. They argue that companies are willing to invest in this sector due to the opportunities for making significant profits, but if exclusive rights were eliminated, they would stop trying to treat rare diseases. It should also be borne in mind that there are enormous risks in this sector, so that for every company that makes huge profits, dozens of others will fail. Individual states can also have their own regulations, making it possible to obtain exclusive rights for longer periods; conversely, orphan drug classification may even be revoked. A case in point is a drug used to treat AIDS-related diseases, produced by a company based in North Carolina.

A third case, closely related to the first two, is the "black box" phenomenon, namely the fact that the price of the orphan drug should be proportionate to covering the costs of research and development, but thanks to rules relating to trade confidentiality, this information cannot be divulged and is known only to the company that produces it. Controversy over the very high prices of orphan drugs is commonplace. The latest such dispute involves a drug used to treat spinal muscular atrophy; in the first year of treatment alone the costs amount to $750,000, and in subsequent years and for the rest of the patient's life, they amount to $375,000 per year. Insurance companies refuse to cover these expenses, which means that only wealthy patients can be treated; otherwise public funding must be used. It is true, however, that the pharmaceutical company has introduced ways of providing financial support for patients' families and provides facilities for treating children. Another well-known case is the only existing drug for the treatment of two rare diseases (PNH, paroxysmal nocturnal haemoglobinuria, and AHUS, atypical haemolytic uremic syndrome) and costs each patient half a million dollars every year. On the basis of statements by university researchers who worked on the discovery of the drug, it is thought that around 80% of the research costs for this drug were covered by public funding and that the costs of development and commercialisation amount to about 1% of the sale price of the drug. The public system or the private insurance system can cope

with the huge costs. This drug brought its pharmaceutical company revenues of $6 billion in eight years, making it one of the world's leading companies. Given the high cost, New Zealand's public health system has refused to cover it, and in Canada only a few provinces guarantee public coverage, thus creating a problem of access to medicine and survival for people with these rare diseases. Among other things, it has been found that the annual price of the drug is much higher in Canada than in other countries.

The fourth phenomenon, which also produces major abuse, is so-called 'salami slicing'. The technique involves applying for exclusive marketing authorisation for an orphan drug to be used for a specific rare disease and then, either at the same time or sometime later, applying for the same authorisation for a different rare disease. In this way, a drug can benefit from a variety of monopolistic advantages that can be distributed strategically over time in order to obtain maximum profit and cunningly prolong the exclusive commercial use of the drug.

Despite these abuses, for which the intervention of agencies and institutions working for the protection of competition between companies is required, the regulatory framework introduced has, in reality, produced positive results, as it has given a boost to research into, and industrial production of, drugs that pharmaceutical companies would otherwise have had no economic interest in producing.

3. Comparative notes on countries outside Europe

The second country to introduce special legislation on orphan drugs, with a regulation of 1993, was Japan, which is, one may recall, one of the most industrialised nations in the world.

In Japan, the status of orphan drug is granted to a pharmaceutical when two conditions are fulfilled, namely that it is to be used for incurable conditions for which no alternative health treatments are possible, or for conditions where the effectiveness and reliability of the drug are excellent in comparison with others on the market, and secondly that the number of patients with the condition in Japan be under fifty thousand, i.e., four cases per every ten thousand individuals.

Orphan drug status is granted by a branch of the Ministry of Health, Labour and Welfare, through a subcommittee within the Committee for Medicinal Products, whose conclusions are validated by a special committee. The applicant has to provide the administrative authority with the following data: the estimated percentage of patients in proportion to the overall population, and non-clinical studies and findings relating to the initial clinical phase, as well as the way the protocol has been developed. The authority that grants orphan status may revoke it if the above conditions cease to subsist.

The incentives that the Japanese government grants for research and development on orphan drugs fall into two types. First, they enjoy a simplified marketing authorisation procedure, as the law gives priority to the assessment of applications for the diagnosis or treatment of rare diseases. In addition, the Organisation for Drug Safety and Research advises pharmaceutical companies on the implementation of protocols and the preparation of approved applications. Furthermore, the duration of the industrial patent, which is usually six years for traditional drugs in Japan, is extended to ten years for orphan drugs, there are a number of financial incentives, including subsidies, such as those from the Pharmaceutical Fund for the reduction of side effects and the promotion of research, which provide financial assistance to cover part of the research and development costs of the orphan drug, as well as scientific work and consulting for development, and especially for clinical trials. Reimbursement of costs is available to cover fifty percent of drug development costs. In addition, there are tax incentives consisting of a six percent reduction in taxes for research and development expenses. Pharmaceutical companies that make a profit from the sale of orphan drugs must return part of the subsidies received as a contribution to the preservation of this kind of aid.

Australia has moved in a different direction since 1997-98, when it entered into an agreement with the United States for the exchange of information on rare conditions and orphan drugs. The Australian Therapeutic Goods Administration (TGA) signed an agreement with the US FDA, whereby the former transposes the provisions of the latter, incorporating them into its evaluation process. Specifically, criteria were established for the recognition

and evaluation of drugs not yet screened by the U.S. authorities or that do not meet the criteria established for the United States.

In Australia, the status of "orphan" was initially granted less easily than in other countries, being reserved for drugs to be used for treating conditions afflicting less than 1.2 cases per ten thousand and less than two thousand cases among the total population. New regulations came into force in 2017-2018, introducing amendments to the Therapeutic Goods Regulation of 1990 and providing for a limit of fewer than five cases per ten thousand individuals, a threshold closer to those found in other major industrialised countries.

Orphan drug status is valid for six months, and an extension may be requested every six months in order to keep the administrative offices up to date. This status entitles the holder to fiscal advantages (the TGA waivers dues for applying for marketing authorisation and the annual registration fee). There are also financial perks (the TGA covers the costs of the process of designating a drug as orphan, compensating for the costs incurred via other items in the health budget), as well as privileged patent rights (the monopoly lasts five years).

Among non-European countries, South Korea, Singapore, and Taiwan have also adopted specific regulations for orphan drugs. There is an enormous gap between richer and more industrialised countries and poorer and less well-equipped ones in terms of health protection. Notably, no specific public policies on orphan drugs have been developed on the African continent. The situation is particularly delicate for so-called "orphan vaccines", i.e. those used to treat rare infections or those with limited territorial impact (namely those affecting a limited geographical area but a very large number of people living there): the risk is particularly high for pharmaceutical companies, which would face development and research costs impossible to recover from product sales. If economic factors are negative, the incentive for a pharmaceutical company to work on an orphan vaccine may be dictated by non-economic motives, such as, for example, the decision to promote an ethical company image or else it may reflect a strategic choice by the company as a whole. Aid strategies may be implemented by richer countries or supranational bodies on the political level, or they may be inspired by humanitarian concerns through private donations, and they often work together.

For this, however, there is no supranational organisation to shoulder the task of coordinating the various policies in such a way as to concentrate energies on achieving the most important goals.

4. Orphan drugs in European legislation

European Orphan drug regulation came about almost 20 years after U.S. regulation and was clearly inspired by it. The recognition of orphan drug designation takes place through an administrative procedure governed by European Regulation No. 141/2000, which involves the European Medicines Agency (EMA) and the Committee for Orphan Medicinal Products (COMP), established within it[24].

Indeed, in order to qualify a medicine as "orphan", the sponsor (almost always the manufacturer) applies to European Medicines Agency at each stage of the drug development process (but still prior to marketing authorisation). After an initial assessment of the admissibility of the application, the Agency sends a summary report to the Committee for Orphan Medicinal Products, which must reach an opinion on the recognition or otherwise of the designation of the drug as "orphan" within ninety days of receipt of the application. This opinion is then sent to the European Commission, which adopts a decision recognising the designation or rejecting the application within 30 days of receipt.

Under Article 8 of the Regulation, "the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization or grant a marketing authorisation or accept an application to extend an existing marketing authorisation for the same therapeutic indications in respect of a similar medicinal product with for a period of ten

[24] As stated in Article 4 of Regulation (EC) No. 141/2000, the Committee is composed of one member appointed by each Member State, three members appointed by the European Commission to represent patients' organisations, and three members appointed by the Commission on the basis of the Agency's recommendations. The term of office lasts three years and is renewable.

years"[25]. This will ensure that the orphan medicinal product will have exclusive production for a period of one decade.

Regulation (EC) No. 726/2004 requires certain types of medicinal products, including orphans, to be subject to a "centralised" procedure in order to obtain marketing authorisation.

This procedure is carried out by the EMA through its Committee for Human Medicinal Products (CHMP). The Committee, after scientific assessment of the documentation submitted by the applicant, issues an opinion which is then forwarded to the European Commission. The Commission then adopts a decision that becomes binding on all Member States. The centralised procedure must be completed within two-hundred-and-ten days.

In Italy, the European Assessment Office plays an important role with regard to medicines authorised through the centralised procedure. It works through the *AIFA*, which carries out a scientific assessment of the dossiers of innovative medicinal products of high technological value.

This office classifies these drugs in a special section dedicated to pharmaceuticals that have not yet been assessed for reimbursement [class C(nn)], issuing a resolution of transposition to that effect. This class, established by Law No. 189/2012, can be considered provisional and includes drugs not yet assessed for reimbursement.

EC Regulation No. 141/2000 on orphan medicinal products now made it possible for companies manufacturing these products to request a prior opinion from the EMA on the various tests and trials necessary to demonstrate the quality, safety and efficacy of the drug; the Regulation also provides for the establishment of a procedure for the development of orphan drugs, consisting of

[25] Before applying for marketing authorisation, the sponsor of an orphan medicinal product may request an opinion from the Agency on the performance of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product under Article 51(j) of Regulation (EEC) No. 2309/93. 2. The Agency establishes a procedure for the development of orphan medicinal products, including normative consulting to define the content of the application for authorisation in accordance with Article 6 of Regulation (EEC) No. 2309/93.

regulatory advice from the Agency regarding the definition of the content of the application for authorisation.

Furthermore, on the basis of this Regulation, European Union – and consequently the Member States – undertake not to grant or accept other marketing authorisations for similar medicinal products with the same therapeutic indications for a period of ten years, thereby guaranteeing a period of protection.

In order to encourage the production of orphan medicinal products, the European Union has made it possible, for certain categories of medicinal products responding to unmet medical needs, to grant marketing authorisation more quickly, based on data less complete than those normally required. For this, there exist a conditional marketing authorisation and a marketing authorisation granted in exceptional circumstances.

In order to strike the right balance between reducing the time needed to access medicinal products and authorisation for medicinal products based on an unfavourable risk-benefit balance, it is necessary to subject these marketing authorisations to specific obligations. The holder should complete or undertake certain studies to confirm that the risk-benefit balance is favourable and to resolve any doubts regarding the quality, safety, and efficacy of the product.

Conditional authorisation, governed by Regulation (EC) No. 507/2006[26], consists of the rapid approval of a drug on the basis of less complete clinical data than those generally required. This form of authorisation may be required for a medicinal product intended for an unmet medical need, a seriously life-

[26] According to point 2 of the Preamble to Commission Regulation (EC) No. 507/2006 on a conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004, "In the case of certain categories of medicinal products, however, in order to meet unmet medical needs of patients and in the interests of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally the case and subject to specific obligations, hereinafter conditional marketing authorisations. And, according to point 6 of the Preamble, In the case of the conditional marketing authorisation, authorisation is granted before all data are available. The authorisation is not intended, however, to remain conditional indefinitely. Rather, once the missing data are provided, it should be possible to replace it with a marketing authorisation which is not conditional, that is to say, which is not subject to specific obligations".

threatening or disabling condition, a rare disease, or for use in emergency situations in response to a threat to public health.

Conditional marketing authorisation may be issued if the Committee considers that, although full clinical data on the safety and efficacy of the medicinal product have not been provided, the risk-benefit balance of the medicinal product is nevertheless respected, it is likely that the applicant will be able to provide full clinical data at a later date, that the medicinal product is intended to meet unmet medical needs, and that the public health benefits deriving from the immediate availability on the market of the medicinal product in question outweigh the risk arising from the fact that additional data are still needed.

This authorisation is valid for one year and may be renewed. The company developing the drug is required to conduct further studies to provide complete data so that the conditional authorisation can be converted into a standard one. Authorisation is granted in urgent circumstances and may be granted on condition that the applicant puts mechanisms on the safety of the medicinal product in place and informs the competent authorities of any drawbacks related to the use of the product.

Conditional authorisation issued in exceptional circumstances, generally meaning extremely rare diseases[27], is different from conditioned marketing authorisation. Both procedures are laid down in Article 14 of Regulation (EC) No. 726/2004, (7) and (8) respectively. However, while conditional marketing authorisation is issued before all the data are available, and will subsequently be supplemented by the missing data, it

[27] Article 14(7) of Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, which provides that "Following consultation with the applicant, an authorisation maybe granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible. By way of derogation from paragraph 1, such authorisation shall be valid for one year, on a renewable basis. The Commission shall adopt a Regulation laying down provisions for granting such authorisation. That measure, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87 (2a)".

will never be possible, in principle, to compile a complete dossier for marketing authorisation issued in exceptional circumstances.

5. Italian regulation

In Italy, the European tendency to facilitate rapid entry onto the market of the drug and, therefore, simplified access to orphan drugs, is confirmed[28]. Law no. 189/2012 made it possible for a pharmaceutical company to apply to the *AIFA* for pricing and reimbursement immediately after the issue of the CHMP's positive opinion and therefore even before the European Commission has issued a Community authorisation to market the drug. This exception to the normal procedure is not only reserved to orphan drugs but also those that can only be used in a hospital environment and drugs of exceptional therapeutic importance. With subsequent Law No. 98/2013, the *AIFA* was assigned the task of assessing orphan drugs of exceptional therapeutic importance as a matter of priority, with a maximum evaluation time of one-hundred days (so-called "fast track" authorisation)[29].

[28] For an overview of the regulation of drugs in Italy, see, *ex multis*, M. Gnes, *Farmaci*, in M.P. Chiti, G. Greco (eds.), in *Trattato di diritto amministrativo europeo*, *Parte speciale*, (2007), 1075-1111; C. Casonato, *I farmaci, fra speculazioni e logiche costituzionali*, in 4 Rivista AIC 1 (2017); about the legal regulation of orphan drugs in Italy, see, among others, F. Ficicchia, *Malattie rare e farmaci orfani. Profili giuridici*, in 4 Contratto e impresa. Europa 428, 458 (2007); F. Massimino, *Qualifica di "medicinale orfano": condizioni per l'assegnazione e giurisprudenza del Tribunale di primo grado*, in 1 Diritto pubblico comparato ed europeo 167, 171 (2011); A. Magni, *I c.d. "diritti della personalità", il diritto alla salute e le c.d. "malattie rare" nell'ordinamento Italo-europeo*, in 5-6 Il Diritto di famiglia e delle persone 1152, 1164 (2016); A. Parziale, *Il futuro dei farmaci orfani tra promozione della ricerca per la cura di malattie rare e i rischi di prezzi eccessivi: il ruolo del diritto della concorrenza*, in Contratto e impresa 1245,1277 (2016); G. Sena, *Farmaci "orfani" e medicinali per uso pediatrico. Note critiche*, in 1 Rivista di diritto industriale 173, 178 (2016); A. Perfetti, *La tutela della salute nell'Unione europea attraverso l'azione nel campo delle malattie rare*, in 1 DPCE online 18 (2017); L. Scaffardi, G. Formici, *Farmaci orfani nel panorama europeo e nazionale: alla ricerca di un delicato equilibrio*, in 1 Amministrazione in cammino 1 (2017); A. Cauduro, *Il paradigma del farmaco orfano*, in Costituzionalismo 55,70 (2018); A. Magni, *Il diritto alla salute e la creazione di sottogruppi: riproposizione di principi attivi già approvati e autorizzati nell'ambito della terapia delle c.d. "malattie rare"*, in 3-4 Il Diritto di famiglia e delle persone 305,324 (2019).

[29] Pursuant to Article 44(4-ter) of Decree Law No. 69/2013 (converted into Law No. 98/2013), amending Law No. 189/2012 with the introduction of Article 5-

Products designated as "orphan medicinal products" are entered in a European register and, if authorised to be placed on the market, are eligible for a special preferential scheme designed to compensate the producers of any medicinal products for the diseconomies they have suffered and that are not offset by sales profits. Marketing authorisation for orphan medicinal products follows the same rules as any other medicinal product[30]. In the case of orphan medicinal products, however, pursuant to Article 7(1) of (EC) Regulation No. 141/2000, the applicant may be exempted from the obligation to demonstrate the requirements set out in Annex B to (EEC) Regulation No. 2309/1993, namely that the medicinal product be of "major therapeutic interest" and constitute "a major innovation". In the Communication from the Commission on the application of Articles 3, 5, and 7 of EC Regulation No. 141/2000 on orphan medicinal products, and in particular in relation to the relationship between orphan and non-orphan medicinal products, paragraph D states that the procedure for designation as an orphan medicinal product and for marketing authorisation are "governed by different criteria, which means that different decisions may be taken as regards, for example, the condition underlying the designation and the authorised therapeutic indication".

The main benefit provided for by the European Regulation is that it is possible to grant the designated orphan medicinal product exclusive access to the market throughout Europe for a period of ten years[31]; moreover, under Article 9 of the Regulation,

bis, the *AIFA* assesses, for the purposes of classification and reimbursement by the National Health Service, the medicines referred to in paragraph 3, for which the relevant application for classification referred to in paragraph 1 has been submitted, accompanied by the necessary documentation as a priority and giving them priority over the classification proceedings pending at the date of submission of the application referred to in this section, including through the establishment of extraordinary sessions of the competent Commissions. In this case, the period referred to in the first sentence of paragraph 4 is reduced to one hundred days (so-called fast track authorisation).

[30] The framework was initially contained in Council Regulation (EEC) No. 2309/1993. Subsequently, Directive 2001/83/EC on the Community code relating to medicinal products for human use was adopted.

[31] That market exclusivity referred to in Article 8 of EC Regulation No. 141/2000 is not the same as patent exclusivity, which may protect the same product at the same time, since the European regulation is without prejudice to the legislation on the protection of intellectual property. On this point, see G.

designated orphan medicinal products "may benefit from incentives made available by the Community and the Member States in order to promote research, development and placing on the market".

Many drugs have been designated as "orphan" up to now, meaning they have completed the procedure to ascertain their necessity in the treatment of a condition considered serious and rare. In fact, there are over one-thousand-two-hundred of them. However, of the drugs that have obtained this designation, only slightly more than a tenth have gone on to receive marketing authorisation: this testifies to the level of risk associated with developing orphan drugs.

Recognition of the designation of orphan drug is not the desired outcome of research and testing geared to treating previously untreated diseases. It is actually an intermediate phase, following the identification of a drug suitable for the treatment of a serious and rare condition not previously treated, but prior to further testing, consisting of pre-clinical and clinical studies, after which it will be possible to apply for marketing authorisation for the drug. Statistically, it is during this phase that a drastic reduction in the number of orphan drugs eligible to be marketed occurs.

To date, just under one hundred orphan drugs have been authorised and reimbursed in Italy, making up 73% of those approved in Europe. Public health expenditure for orphan drugs has almost tripled in recent years, rising from six-hundred-and-fifty-million in 2010 to one-billion-six-hundred-million in 2017.

6. Incentive measures for pharmaceutical companies operating in the orphan drugs sector: comparative profiles

Measures such as granting a temporary monopoly or agreeing on a high price for the orphan drug aim to encourage pharmaceutical companies to invest large sums in research and development, substantially compensating for the risk of losing the money invested: the research may not bear fruit (as the cure may not be found), or once the cure is found, it may not be recognised

Sena, *Farmaci "orfani" e medicinali per uso pediatrico. Note critiche,* in 4-5 Riv. dir. industr. 173 (2016).

as an orphan drug, or authorisation to market the drug may not be granted. The sector is therefore subject to a high degree of uncertainty.

However, this need is hindered by the necessity of containing public expenditure and the need not to place an unlimited economic burden (inevitably growing and not wholly predictable) solely on the State budget and therefore on society as a whole.

Within the European scenario, the measures adopted by the individual States to compensate for the greater economic burden placed on them by the process of research and development related to medicines for rare diseases are diversified. Examining the regulations adopted in the various European countries to implement Regulation (EC) No. 141/2000, we can distinguish between measures that constitute incentives and funding for research (Cyprus, Poland, Spain), the provision of dedicated funds for spending on orphan drugs (Croatia), reimbursement measures from public funds (Estonia, Greece, Poland) or through the insurance system (Germany, Slovakia), tax exemptions for companies producing orphan drugs (France), and the joint negotiation of pricing by pharmaceutical companies and the State (Belgium, the Netherlands and Luxembourg)[32].

As mentioned above, in the United States, the ODA introduced a series of tax reliefs for pharmaceutical companies and various forms of incentives (e.g., research funding or covering the costs of experimentation and development), as well as forms of temporary market monopoly (lasting seven years) provided for by law and authorised by the FDA.

All these mechanisms confirm the need to guarantee that the economic operators working in this sector receive some form of support regardless of the market dynamics in order to guarantee patients suffering from rare diseases their right to health.

The solution adopted in Italian legal system is based, on the other hand, on a payback principle, i.e. the distribution of costs among pharmaceutical companies when they exceed the budget

[32] Please refer to 2015 European Commission document, "Inventory of Union and Member State incentives to support research into, and development and availability of, orphan medicinal products", SWD (2015) 13 final.

allocated to the national health fund by the State. On the other hand, this mechanism, which is applied in general to all annual pharmaceutical costs, contains a special provision reserved for pharmaceutical expenditure for orphan drugs for hospital use, which far exceeds that for prescription use.

This figure, despite contributing to the total national pharmaceutical expenditure, remains distinct from it for the purposes of distributing the associated costs, as any figure exceeding the State coverage ceiling is distributed only among pharmaceutical companies that do not produce orphan drugs (or in proportion to the turnover for non-orphan drugs in the case of companies that produce both types of drugs).

Before describing the mechanism adopted for orphan drugs in Italy, it is necessary to briefly illustrate the essential features of pharmaceutical expenditure coverage.

7. The pharmaceutical expenditure coverage mechanism in Italy

From a reading of the sources that regulate the national pharmaceutical expenditure coverage mechanism, it is clear that the legislator's aim is clearly to "guarantee the balance of the public purse"[33], and "efficiency in the use of resources allocated to the health sector"[34], given the strategic importance of the pharmaceutical sector to the country's industrial and innovation objectives and the contribution this sector makes to health goals in the provision of essential levels of care[35].

To do so, national and hospital pharmaceutical costs are borne by the State up to a pre-established percentage calculated by referring to the National Healthcare Requirement (NHR)[36] forecast

[33] See Article 21 (2) of Decree Law No. 113/2016.
[34] See Article 15 (1) of Decree Law No. 95/2012.
[35] See Article 21 (l) of Decree Law No. 113/2016.
[36] The National Health Requirement is the overall amount of resources of the National Health Service (NHS) to whose funding the State contributes and is established by law on an annual basis. Pursuant to Article 12 of Decree Law No. 502/1992, the *Fondo Sanitario Nazionale di parte corrente e in conto capitale* (National Health Fund for current and capital contributions) is entirely financed by State funds, and is established annually by the Finance Act on the basis of the presumed total amount of sickness contributions allocated to the Regions that year.

for the year of reference. The legislator has changed the percentage of State coverage over the years without prejudice to the different ceilings of coverage for national pharmaceutical and hospital pharmaceutical expenditure.

National pharmaceutical expenditure[37] (now "prescription" expenditure) includes pharmaceuticals supplied according to the rules for prescription medicines but not that for A-class pharmaceuticals supplied directly[38].

For this expenditure, the National Health Service guarantees coverage of costs up to a legally established percentage, which is currently equal to 7.96%[39] of the National Health Fund, corresponding to an amount annually quantified by the Ministry of Health[40]. If this ceiling is exceeded, coverage for the overspend is distributed among the pharmaceutical companies with marketing authorisations for class A pharmaceuticals in proportion to their turnover, as well as among wholesalers and

[37] Total national pharmaceutical expenditure is determined on the basis of data sent monthly by the Regions to the Ministry of Economy and Finance, the *AIFA*, and the Ministry of Health.

[38] See Article 5 (1) of Decree Law No. 159/2007. Pursuant to Article 5(2)d, and Law No. 222 of 29 November 2007, the parameter for monitoring pharmaceutical expenditure under the agreement is the Osmed flow established under Article 68 (9) of Law No. 448 of 23 December 1998, while expenditure for the direct distribution of class A medicines, including distribution upon hospital discharge is recorded on the basis of the flow established pursuant to Ministerial Decree of 31 July 2007 ("Information flow regarding pharmaceutical services provided through direct distribution").

[39] Article 1 (399) of Law No. 232/2016. The legislator has reduced the percentage several times over the last three decades, going from 16% per Region in 2004 (Article 48, Decree Law No. 269/2003) to 14% in 2008 (Article 5(1), Decree Law No. 195/2007), to 13.6% for 2009 (Decree Law No. 232/2016). Decree Law No. 39/2009, converted into Law No. 77/2009), 13.3% for 2010 (Decree Law No. 78/2009 converted into Law No. 102/2009), 13.1% for 2012 (Article 15(2), Decree Law No. 95/2012, converted into Law No. 135/2012), 11.35% provided for in Article 15(3), Decree Law No. 95/2012.

[40] Pursuant to Article 5(1) of Decree Law No. 159/2007, the absolute value of the burden on the National Health Service for the aforementioned pharmaceutical assistance, both at national level and in each individual Region, is to be established annually by the Ministry of Health by 15th November of the year preceding the year of reference on the basis of the allocation of financial resources to the National Health Service approved by the CIPE, or on the basis of the allocation proposed by the Ministry of Health, to be formulated by 15 October.

pharmacies that have supplied pharmaceuticals in category A, this time in proportion to the share of the retail prices of the products that they earn[41].

Hospital pharmaceutical expenditure[42] (now called "direct purchases") is calculated on the basis of the total pharmaceutical expenditure excluding prescription medicines, vaccine costs, paramedicines, officinal preparations for hospital pharmacies, and foreign medicines[43], but including class A medicines distributed directly or on behalf of the company.

Coverage guaranteed by the National Health Service currently makes up 6.89% of the National Health Fund[44]. If this state coverage ceiling is exceeded, 50% of the surplus hospital pharmaceutical coverage is distributed to the Regions where the expenditure ceiling has been exceeded, in proportion to their respective deficits, and 50% to the pharmaceutical companies with marketing authorisation for class H[45] medicines purchased by public health facilities.

For both expenditure flows under discussion, the "ceilings" for State coverage are essentially defined on the basis of previous expenditure calculated for pharmaceuticals and pharmaceutical companies and subject to annual adjustments by the legislator and the administrative authority.

Article 21 of Law No. 113/2016, converted into Law No. 160/2016, regulates the mechanism for covering hospital and territorial pharmaceutical expenditure in excess of State coverage ceilings, establishing a special mechanism for the years 2013-2014-2015 and 2016, in part overlapping with the provisions of Article 5

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41 See Article 5 (3)(a) of Law No. 222/2007. For the share of overspend borne by the distribution chain, the *AIFA* can establish the percentage of discount on sales made in the six months following the effective date of the redistribution measure that will allow the National Health Service to recover the value of the redistribution among pharmacists and wholesalers.

42 This expenditure is calculated from the flow established in accordance with the Ministerial Decree of 31 July 2007.

43 This percentage has seen a significant increase over time, since Article 5(5) of Decree Law No. 159/2007 established a coverage of 2.4%, and Article 15 of Decree Law No. 95/2012 established coverage of 3.5%.

44 Article 1 (1)1 398, of Law No. 232/1016.

45 These are medicines reimbursable by the National Health Service when used in hospitals or similar facilities according to the provisions of the Regions or autonomous provinces, as defined in the *AIFA* Resolution of July 25, 2005.

of Decree Law No. 159/2007. In summary, after provisional quantification of the portion of coverage due to each pharmaceutical company with a medicine marketing authorisation, the *AIFA*[46] approves the final document for monitoring pharmaceutical expenditure, where it ascertains whether the National Health Service has exceeded the ceiling and calculates the final shares of coverage to be distributed among the pharmaceutical companies. In addition, the amount of coverage paid by the pharmaceutical companies the previous year is subtracted from the annual coverage budget, further reducing the margins of expenditure borne by the State.

8. Pharmaceutical expenditure coverage for orphan drugs

This regulatory framework contains a special regulation for expenditure on innovative and orphan drugs.

In the case of innovative drugs[47], pursuant to Article 15(8)(b), Decree Law No. 95/2012, a dedicated guarantee fund was established, details of which are established on a year by year basis[48]. Only when pharmaceutical expenditure attributable to innovative medicines exceeds the amount of the fund does it

[46] The procedure involves pharmaceutical companies, companies specialised in the distribution of medicines, and trade associations, with which the *AIFA* provides data from two separate information flows: the OSMED data flow for national pharmaceutical expenditure, and data from the New Health Information System of the Ministry of Health for hospital pharmaceutical expenditure. They are entitled to submit a request for the data to be rectified before the final measure approving the amounts of coverage for pharmaceutical expenditure is ratified.

[47] These drugs are identified on the basis of three parameters: therapeutic need, added therapeutic value, and the quality of evidence or the robustness of clinical studies. Therapeutic need depends on the existence of therapies for the condition in question and indicates the extent to which the new therapy can give new answers to existing therapeutic needs; added therapeutic value is determined by the extent of clinical benefit brought by the new drug in comparison with the alternatives available, if any; the quality of the evidence is given by the scientific excellence of the elements produced to support innovation. The innovativeness of a drug is recognised by *AIFA*.

[48] The allocation for the years 2015 and 2016 was quantified by Law No. 190/2014.

contribute to reaching the overall pharmaceutical expenditure ceiling[49].

From 2016, national pharmaceutical coverage for innovative medicines is distributed equally among the pharmaceutical companies authorised to market the same innovative medicine and the other companies in proportion to their respective turnover for non-innovative medicines covered by a patent (see Article 5(3)(a), Decree Law No. 159/2007).

As for orphan drugs, hospital pharmaceutical expenditure in excess of the state coverage ceiling is covered by all companies holding marketing authorisation in proportion to their respective turnovers for non-orphan and non-innovative medicines covered by patent (see Article 21(15) Decree Law No. 113/2016)[50].

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[49] Pursuant to Article 1(569) of Law No. 208/2015, "in order to allow the proper administration of innovative drugs in compliance with the planned financial framework for the national health service and in relation to measures to improve the efficiency of the health sector (...) for the years 2015 and 2016, expenditure for the purchase of innovative drugs contributes to reaching the ceiling for territorial pharmaceutical assistance as per Article 15 (3) of Decree Law No. 95/2012, converted into Law No. 135/2012 for the amount exceeding the amount of the fund referred to in Article 1(593) of Law No. 190/2014 for each of the years 2015 and 2016. Article 21 (15) of Decree Law No. 113/2016 establishes that the *AIFA* also determines the coverage of the portion of the amount beyond the ceiling of hospital pharmaceutical expenditure attributable to innovative drugs not complying with the ceiling of the specific fund referred to in Article 15(8)(b) of Decree Law No. 95/2012", "distributing it among all the companies with marketing authorisation in proportion to their turnover for non-orphaned and non-innovative medicines covered by patent. Within the same period, the *AIFA* shall also establish the amount of coverage of the portion in excess of the national pharmaceutical expenditure ceiling attributable to the overrun of the specific fund referred to in Article 5, paragraph 2, letter a) of Decree Law No. 159/2007 by innovative medicines, distributing it among all companies with marketing authorisation in proportion to their respective turnover for non-innovative medicines covered by patents".

[50] The exception for orphan drugs is provided for in Article 15(8) i) and i-bis), Decree Law No. 95/2012, referred to in Article 21(15) of Decree Law No. 113/2016. The explanatory report to Decree Law No. 95/2012, states that "On the basis of current legislation (Article 17(1)(b), Legislative Decree No. 98/2011) the expenditure ceiling for hospital pharmaceuticals amounts to 2.4 per cent and a payback to be paid by pharmaceutical companies if the ceiling is exceeded, equal to 35% of the overspend. The provisions in question replace the provisions of Article 17 (1) (b) in full, recalculating the expenditure ceiling from 2.4% to 3.2%, increasing the percentage of payback from 35% to 50% and excluding certain drugs (vaccines, class C and C-a drugs, foreign drugs, etc.)

In recent years, developments in scientific knowledge, technological equipment (also in the field of medicine), and innovation in research have led to increased levels of health protection and the production and commercialisation of increasingly advanced, effective, and safe drugs, which have, however, contributed to increased annual pharmaceutical expenditure and a consequent burden on pharmaceutical companies.

Consequently, there has also been a gradual increase in expenditure beyond the state coverage ceiling subject to the coverage mechanism: from 2013 to 2016, overspend has risen from 11% to 29% of total expenditure. These percentages include both expenditure for orphan drugs and other types of drugs subject to payback. Concerning orphan drugs, as shown by the 2015 Osmed report, expenditure has risen from €657 million in 2010 (equal to 3.5% of total pharmaceutical expenditure) to €1,393 million in 2016 (or 6.1% of total expenditure) in just five years.

This growth trend might well call for a fresh look at the balance found so far between protecting the health of patients with rare conditions and safeguarding the freedom of pharmaceutical companies required to bear the burden of coverage for them, in order to offset the growing burdens they have to face. For this reason too, it is particularly important to check the ability of a regulatory model drawn up in circumstances in part different from the current scenario to resist in time, checking whether the balance found by the legislator between the different constitutional rights involved is affected by new conditions on the reference market, or if it remains valid regardless of external variables.

In this regard, it is first necessary to examine what makes the regulatory framework special, and which solutions thus result unsatisfactory.

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from the parameters for calculating the level of expenditure. Moreover, 50% of any excess in respect of the ceiling must be paid to the regional authority in proportion to the share of access to their health requirements".

9. The need to contain public health expenditure and the right to health of patients suffering from rare diseases

There is a very close correlation between the possibility of satisfying the right to health of patients suffering from serious and less common conditions and the possibility, for the pharmaceutical companies that produce them, of administering them. When a new orphan drug is placed on the market, a certain number of people suffering from a rare disease (in most cases, between a few dozen and a few hundred, in a country with a population like that of Italy) have prospects of treatment and recovery for the first time.

This means that every orphan drug placed on the market corresponds to an increase in demand and expenditure, as the demand has so far been devoid of adequate supply. However, this increase in expenditure is not, in this case, an exceptional or anomalous circumstance. In some sense, it is the real purpose of the work of the companies working in the sector, namely that their research leads to the identification of a drug able to treat conditions that could not be treated before. Newly introduced orphan drugs are therefore added over time to those already on the market and for which expenditure remains almost constant over time (as rare conditions are normally chronic), necessarily leading to an overall increase in pharmaceutical expenditure. As for orphan drugs, a gradual increase in expenditure is therefore an inevitable (and in a sense desirable) consequence of the research being carried out in this sector, which leads to the discovery of new forms of treatment that did not exist before.

On the other hand, this does not happen with common drugs, because the commercialisation of a new drug on a competitive market determines (or may determine) a shift in preference from drugs already on the market to the new one, with no change in overall spending (the over-budget resulting from the purchase of the new drug is compensated for by the under-budget resulting from abandoning old drugs).

If we neglect what has been said so far, with regard to the need to contain public expenditure it might be said that the main cause of exceeding State budgeting for coverage lies with orphan drugs, so intervention is needed in order to ensure a constant balance between the opposing needs of public finance and health protection. However, this would mean ignoring the fact that

increased expenditure in this sector is non-reducible and completely predictable characteristic rather than a disaster to be corrected. Conversely, limiting pharmaceutical expenditure for orphan drugs would mean a reducing research activity on new orphan drugs, i.e., a limitation of the right of people with rare conditions to receive, or at least hope to receive, adequate treatment like anyone else suffering from common illnesses for which drugs are available.

The characteristics described so far make it impossible to apply the same methods of coverage of pharmaceutical expenditure envisaged for normal drugs to orphan drugs.

Article 21 (7), of Decree Law No. 113/2016 states that the *AIFA* has to allocate a portion of coverage to each pharmaceutical company considering all the products that the company is authorised to place on the market. This quota is calculated "on the basis of the turnover for the year prior to the year reference for each pharmaceutical company, increased or decreased according to the percentage variation between the figure established as the pharmaceutical expenditure ceiling of the year when the quota was allocated and the pharmaceutical expenditure resulting from the documentation produced for the previous year".

In the case of orphan drugs, this method of calculating coverage is not applicable. Firstly, in the case of orphan medicinal products, setting an expenditure ceiling or laying the burden of overspend costs on the manufacturers themselves would simply discourage the development and commercialisation of orphan medicinal products, thus going against the provisions of the European regulations and Italian legislation. Secondly, in the case of orphan drugs, it is not possible to take previous pharmaceutical expenditure as a benchmark for calculating the share of coverage to allocate, as the demand for existing orphan drugs (generally used to treat chronic diseases) is supplemented each year by the demand coming from newly diagnosed patients and for newly marketed orphan drugs, which is satisfied for the first time, implying a steady increase in expenditure.

Thirdly, it should be remarked that the minute number of patients leads to discernible market variability for each orphan drug, because the addition or loss of even one patient can result in very high fluctuations in sales history. For this reason, it is particularly difficult to make expenditure forecasts for the

purpose of allocating suitable funds. Similarly, it is impossible to calculate coverage by considering the percentage variation between the figure established for the pharmaceutical expenditure ceiling in the year of allocation of the quota and the pharmaceutical expenditure resulting from the documentation produced for the previous year.

Lastly, even if the company were to comply with cost constraints, this would be tantamount to placing a limit on the number of patients suffering from rare diseases to be treated in the absence of an alternative offer to make up for the failure to supply the orphan drug. In the case of ordinary pharmaceutical supplies, given that there is usually competition between different manufacturers, should a company that has reached its budget not wish to supply a certain drug to the very end, other operators can step in. This is does not happen with orphan drugs, where market exclusivity normally means that only one company producing a given drug is registered. It follows, therefore, that once its budget is reached, an orphan drug marketing authorisation holder would have no economic reason to continue to accept orders. Supply would then only be ensured if a pharmaceutical company voluntarily gave up its own profit (for ethical reasons), apart from an imposed financial obligation. Both solutions are, however, impossible: the first one because the protection of the right to health of citizens cannot be left to the liberal concession of a private entrepreneur, and the second because it is incompatible with the Italian legal and constitutional system[51].

It should also be pointed out that from a quantitative and statistical point of view, the growing economic burden on pharmaceutical companies subject to the coverage mechanism is due to an increase in pharmaceutical expenditure across the board, not only in respect of orphan drugs, which continue to represent a rather low percentage. For the same reason, the onerousness of the payback mechanism imposed on companies

[51] On the subject of the regulation of payback see T.A.R. Lazio, Rome, Sec. III-quater, No. 6173/2015, "Naturally, for the sake of the constitutionality of the entire system, in no way – once a supply contract has been entered into – can a company be obliged to provide a service of indefinite content or, in any case, liable to exceed the limits contractually laid down thereto as that this would result in an imposed service going against the limits mechanism for hospital pharmaceutical expenditure established by the legislator".

would not anyway be reduced if the special regulations were eliminated and the general criterion for the coverage of hospital pharmaceutical expenditure were extended to orphan drugs.

Assessing the possible impact of a possible extension of the payback system currently applied to hospital pharmaceutical expenditure for orphan drugs to orphan drug manufacturers, on the basis of the documents made available by a company and based on data from 2013 (the last officially available), it can be assumed that the median figure[52] would be as follows: companies should return 12% of their turnover, a very high percentage in comparison with the average payback levels for other pharmaceutical companies, which are much lower. It would also be not uncommon for companies to be required to pay more than 25% of their revenues. It is clear that such a mechanism would act as a disincentive to the production of new orphan drugs and, for companies already on the market, would prevent the treatment of a greater number of patients.

It follows therefore that the coverage mechanism for ordinary pharmaceutical expenditure requires different corrective measures than those in place for the coverage of orphan drug expenditure. The mechanism adopted by the Italian legal system requires that, once the ceiling for coverage by the State has been exceeded, hospital expenditure must be covered jointly by the pharmaceutical companies that produce non-patented non-orphan drugs, which are therefore not damaged, for the reasons mentioned above, by the fluidity of the market and the unpredictability of research costs and profits.

It is therefore necessary to verify whether the constitutional bases for this form of regulation are able to guarantee its continuity over time, regardless of any change in real-world circumstances.

[52] The "median" value rather than the "mean" value is used, since it is more suitable for intervals with a wide dispersion of values. If payback were applied to orphan drug manufacturers, around two thirds of them would be affected.

10. The non-reducible core of the right to health in the case law of the Constitutional Court

The rationale of the current regulation on orphan drugs has been analysed above. Specifically, it emerges that the exemption of this category of drugs (and the companies that produce them) from certain mechanisms for the containment of public health expenditure (especially "payback") is the prerequisite for allowing, on the one hand, future patients suffering from rare conditions, for whom adequate drugs are already available, to receive assistance on a par with those already receiving treatment without the risk of being subjected to limitations or quotas. On the other hand, it would allow research institutions and pharmaceutical companies to continue developing scientific research on rare conditions still deemed incurable or not adequately treatable, so that new and useful drugs may be developed.

Having ascertained the usefulness of the current legislative framework, it is also necessary to verify its constitutional necessity, necessarily following two trajectories. First of all, it must be ascertained whether there is any obligation (unavailable, in theory, even from the legislator), on the part of the National Health System as a whole, to endow companies holding marketing authorisation with the sums negotiated with no ceiling for orphan drugs.

Secondly, it needs to be considered whether the resulting burden must be borne by the public sector or may continue to be borne – as the law currently stands – by other private economic operators and, if so, within which limits. The first problem will be addressed in this section and the second question in the next one.

It must be recognised that, where the issue is considered solely from the point of view of the companies that market orphan drugs and the interest of which they are the bearers, it is difficult to establish any non-reducible right on their part not to have to face – in absolute terms – reductions in their revenues.

For reasons that (for a different purpose) will be discussed in the next section, in the "administered market" of medicines, neither the principle of freedom of economic enterprise protected by Article No. 41 of the Constitution nor the principle of protection of legitimate expectations, deriving from Article No. 3 of the Constitution, absolutely prohibit the legislator from

impinging on the expected profit margins of pharmaceutical companies, naturally within the limits of reasonableness. On the subject of obligatory discounts on the prices of drugs reimbursed by the national health service, suffice it to quote a judgment handed down by the Constitutional Court, Judgment No. 279/2006, according to which, the sphere of private autonomy does not receive absolute protection from the legal system, so any disputed constraint in the determination of price is not constitutionally illegitimate when it proves to have been wrought to allow the simultaneous satisfaction of a plurality of constitutionally significant interests.

However, in the subject matter presented, a number of conclusions may be reached, considering the impact of possible changes to the current legislative framework for orphan drugs on citizens' health. Indeed, for the reasons set out above, the main negative effect of the possible application of spending caps in connection with rare conditions would seem to be that it would jeopardise the system of production or distribution of effective drugs for all those in need of them (see also below).

This connection, however, is not a mere *de facto* consequence of a legislative amendment (as such constitutionally irrelevant), but would be a direct effect and an immediate corollary of it. Moreover, this connection was positively and expressly acknowledged in parliament and was the main and declared reason, during the law-making process, for exempting orphan drugs from payback, especially when the Stability Law for the year 2014 was adopted, which makes it possible to discount one argument that draws on the case law of the Constitutional Court on the subject.

Quite recently, with a Judgment of 2006 (No. 203/2006), the Constitutional Court rejected the possibility that Article 32 of the Constitution (on the right to health) might represent a ground for challenging a legislative measure that did not aim directly to regulate the treatment rights of patients, but rather concerned the economic operators of the national health service. In this case, it concerned legislative measures for the "reduction of the outlay and corresponding volumes of purchase" by private bodies authorised to provide care services). However, the Court based its decision on a precise factual supposition, namely that "there is no evidence that the right to health of citizens is affected by the rule"

(since the benefits can be provided in other ways). In the case of orphan drugs, on the other hand, the direct impact on the consideration payable is expressly acknowledged by the legislator itself.

Having clarified this point, one can consider the obligations arising from Article No. 32 of Constitution with regard to the right to health and, more specifically, the right to health care. The question has been the subject of numerous rulings by the Constitutional Court and the Courts of Legitimacy in the most general terms and has been amply addressed in the legal literature.

However, some preliminary caveats are also in order. Not even the right to health, like any other right to protection by the State, can be wholly exempt from balancing with other principles and requirements of constitutional rank, especially to the ends now of greatest interest, with restrictions of a financial nature under Article No. 81 of the Constitution. In the light of the scarcity of resources or, at any rate, of available ones, the allocation of one subsidy may prove incompatible with another, even if equally worthy of protection and consideration.

Hence the principle repeatedly reaffirmed by the Constitutional Court, that "health protection cannot but be affected by the circumstances that the legislator itself encounters in distributing the financial resources available to it" (Constitutional Court Judgment No. 203/2016). It follows that, in general, the right to health care "is guaranteed to every person as a constitutional right conditioned by the implementation that the legislator works through the balancing of the interest protected by that right against other constitutionally protected interests, bearing in mind the objective limits that the legislator encounters in relation to the organisational and financial resources available to it at a given moment" (consolidated case law, at least since Constitutional Court Judgment No. 455/1990: see, among many others, Judgment No. 432/2005, No. 267/1998, No. 304/1994, and No. 247/1992).

Ordinarily, therefore, the constitutional right to health treatment is conditioned by the necessary intermediation of Parliament and is not a "full and unconditional" right *a priori* but becomes so following legislative intervention ("to the extent that the legislator, through a not unreasonable balancing of

constitutional values and the proportionality of the objectives consequently determined by existing resources, ordains adequate opportunities to have access to health care": Constitutional Court Judgment No. 304/94; with opportune "determination of the instruments, times and methods of implementation": Judgment. No. 455/1990).

All this, however, does not imply unconditional discretion at the hands of the legislative power with regard to identifying the health treatments that can be provided; nor can financial requirements be used to indiscriminately reduce the right to health of citizens at will. On the contrary, the Constitutional Court subjects legislative regulation to checks of the double cascade type.

On the one hand, the Court reserves "external" control over the correct "balancing of the constitutional values that the legislator carries out in implementing the right to health care" to itself. This, in particular, is to ascertain that the albeit justified "requirements relating to the equilibrium of public finance" do not assume "an absolutely preponderant weight", a symptomatic indicator of being "presented with a plainly unreasonable exercise of legislative discretion" (Judgment no. 260/1990).

On the other hand, the Court sets a peremptory limit to the same legislative discretion, excluding any possible balance with other values or needs: the guarantee of "an inalienable and Constitutionally protected core consisting of the right to health as an inviolable domain of human dignity that requires the pre-empting of situations without protection and that may undermine the implementation of that right" (among many, see No. 509/2000, No. 252/2001, No. 432/2005; and similar, No. 354/2008, No. 299 and No. 269/2010, and No. 61/2011; the Court sometimes adopts similar expressions, such as "essential", "irreducible" or "non-reducible" nucleus).

The case law of the Italian Supreme Court also follows this line of interpretation. It is now an *acquis*, in the precedents of the Italian Supreme Court, "that health has acquired the qualification of a subjective, fundamental and absolute right, and it has been added that at present a "solid nucleus of the law" has been identified that cannot be suppressed whatever the needs of the community, imposed by the very principle of social solidarity"

(according to a recent and well-known pronouncement of the Joint Civil Sessions in Judgment No. 174611/2006).

It follows that the right to health "stands above the administration in such a way that it has no power, even for reasons of particular public interest, not only to weaken it, but even indirectly to prejudice it in point of fact", because by affecting a fundamental right, the Administration "acts in point of fact", since "its power on this matter cannot be legally configured" (Judgment No. 17461/2006, cited above; and in the same vein, Joint Sessions, Judgment No. 20922/1992). Ultimately, a "constitutionally protected right with a rigid core" emerges, one that "cannot be definitively sacrificed or compromised", in the face of which the public authorities have only the task of the mere practical verification of the conditions that make protection indispensable, with no possible balancing of different interests.

Although these principles are affirmed in relation to the administrative authorities, the Court infers them directly from constitutional constraints (and on the basis of constitutional case law) and they are therefore well equipped to oppose legislative power too.

Having thus framed the conceptual terms, a further analytical effort is now required in order to consider, in particular, the cases examined by the Constitutional Court in order to identify the boundaries of the "essential, non-reducible nucleus" of the right to health and to verify whether it can be invoked in the case presented today.

As might be imagined, the cases concretely taken into consideration by the Judge's ruling on legislation are very diversified.

For example, the Constitutional Court held that it is not possible to infer from the "core" of the right to health (among other things) the universal provision of so-called additional services not directly provided for as essential at national level but at Regional level (Judgment No. 455/1990): voluntary recourse to "indirect assistance" (i.e. in private centres) for continuous or prolonged rehabilitation services, where (albeit under different conditions) they are available in public ones (Judgment No. 304/1994); reimbursement for treatment abroad for contingent reasons by financially able individuals or those with spending limits (Judgment No. 247/1992); the right to receive treatment

under particular conditions (with reference to thermal treatments, heliotherapy and so forth: Judgment No. 559/1987).

On the other hand, the Court held that the irreducible core of the right to health was particularly compromised by the exclusion of reimbursement for essential diagnostic services, albeit costly ones, with facilities holding external contracts, if the public ones were not supplied with the same equipment, whenever "particular conditions of necessity that cannot otherwise be resolved" or "treatments and interventions that cannot otherwise be fulfilled"; other cases are the exclusion of the reimbursement of expenses incurred in private centres, in the absence of prior authorisation, whenever there are "conditions of utter urgency" (Judgment No. 267/1995 and No. 509/2000), and the exclusion from clinical trials of new drugs "in urgent cases of extreme therapeutic need without alternative solutions", when "it is unacceptable, by virtue of the principle of equality, that the material enjoyment of this fundamental right depends on the different economic conditions of the individuals concerned". In such cases, "from the point of view of the constitutional guarantee of health as a right [...], neither the establishment of reduced sales prices for medicinal products [...] nor the allocation [...] of a sum apportioned to municipalities [...] for the support of indigent persons" (Judgment No. 185/1998) appear to be adequate solutions; more generally, in any case, the provision of so-called life-saving therapy is prejudiced.

It is therefore clear that the cases examined are varied and far from homogeneous; nevertheless, some interpretative constants do seem to emerge. The "non-reducible nucleus" of the right to health (which allows of no balancing) is recognisable under the following conditions: the objective gravity of the condition; the *urgency* of or the absolute *need* for the treatment; the unsustainability of the cost for the patient, or the *unsuitability* of alternative treatments on a clinical or organisational level.

Under such conditions, the public authorities have a constitutional obligation to ensure that health care is provided, otherwise they would be exposing the patient to an "absolute lack of protection" (Judgment No. 309/1999). Expressed with regard to innovative treatments, the obligation set out in Article 32 of the Constitution emerges "in relation to patients suffering from conditions" for which "there are no other valid treatments using

drugs or treatments already authorised for these conditions", while "in other cases, namely when there is the possibility of a treatment already tested and validated, any claim that the State must still be required to provide other medical services, even if only hypothetically effective, free of charge would not be reasonable" (Judgment No. 185/1998).

Albeit with some necessary amplifications outlined below, the subject of orphan drugs appears to meet the constitutional requirements set out so far. The prerequisites of the special legal framework more amply described above are, in fact, the particular gravity of the condition to be treated (such as causing danger to life or seriously disabling chronic disorders, thus making treatment both indispensable and urgent), the absence of serious alternative interventions, both on the clinical level (because, by definition, there are no other suitable drugs for treatment on the market, as the law does not allow, in such a case, a drug to be classed as orphan), and from the financial point of view (because the rarity of the disease makes any return on investment highly uncertain, so that, given the absence of a clear and guaranteed legal framework, it is unlikely that a pharmaceutical industry will invest in the sector), the impossibility for citizens to bear the cost of providing health care (because, once again, the rarity of the disease makes it difficult to amortise the costs of research and development of the drug, leading to an inevitable increase in the cost of individual treatment).

In other words, the current legal framework on orphan drugs seems to be designed expressly to protect the essential and irreducible core of the right to health of patients suffering from rare conditions. This is achieved through the inclusion of a series of derogations, prerogatives and incentives, necessary and sufficient to counterbalance (or at least reduce) the diseconomies that would otherwise inevitably arise in scientific research and the treatment of rare diseases.

This does not rule out, of course, that in the abstract, equivalent regulatory solutions may be found that would be able to produce an equal degree of defence for the protected interest (which, it must be reiterated, is directly that of patients and only indirectly that of companies holding marketing authorisation in the orphan sectors).

11. The balance of the current distribution of expenditure, borne jointly by public and private economic operators

In view of the impossibility of denying protection to patients suffering from rare diseases by setting limits on the cost of orphan drugs, it is necessary to verify whether the coverage of such charges must in fact be borne by the public sector or whether it can (and to what extent) continue to be borne by other private economic operators, as established by the current provisions.

In this regard, two elements have to be considered: the need to ensure the containment of public spending (and therefore not to lay the entire burden of pharmaceutical expenditure on the public purse) and, on the other hand, the right of pharmaceutical companies not to suffer unjustified prejudice to their freedom of enterprise.

The following aspects thus need to be assessed: whether there is a constitutionally supported criterion whereby the sacrifice of a specific category of economic operators for the sake of the public interest in containing expenditure is not only allowed but also necessary, and what the conditions necessary for this sacrifice to take place are, all the while respecting the principle of proportionality and non-discrimination. Furthermore, it must be assessed whether this sacrifice continues to be justified, also in the light of the constitutional principles, despite the increase in pharmaceutical expenditure on orphan drugs.

In order to examine these aspects, on the one hand, the experience of other sectors (relating to the provision of services of general economic interest) in which the obligations of universal service are covered by forms of compensation between all the operators would appear particularly useful as would the conclusions that have become consolidated in case law regarding the regulation of obligatory discounts on the negotiated price of medicines (the effects of which can be likened, for our purposes, to the current legislative framework on containment), imposed on pharmaceutical companies and wholesalers[53] to safeguard the objectives of containing public spending[54].

[53] See F. Sorrentino, *I principi costituzionali che regolano i prezzi dei farmaci*, in *Seminari di studi giuridici in materia di farmaci* (1995), "The reference to Article 32 of the Constitution takes on different meanings. With regard to prices it may justify the possibility for the State to impose 'discounts' on companies as an exception to the provisions on general price regulation. The discount

Of course, a number of essential public services have been affected by processes of opening up to competition law. If market logic were strictly applied in these sectors, access to essential services would be precluded to a wide range of citizens, especially the weakest and most needy, if, for example, they reside in sparsely populated areas or areas that are more difficult to reach, or find themselves in economic or social difficulties. The European legal order, based, among other things, on the principles of social and territorial cohesion and solidarity, stipulates that the community should be guaranteed access to these essential services, even if doing so does not meet economic criteria and, therefore, there is no economic return for the company providing the service. In this case, although the service provided cannot be remunerated, Member States may impose public service or universal service obligations on operators.

The concept of universal service is particularly important in certain service sectors of general economic interest, such as electricity, postal services, rail services, and electronic communications, and this, perhaps, is the most noteworthy. The public service obligations that must be guaranteed to all users include, among other things, telephone line connection and an Internet service with a connection above a certain transmission speed.

Operators providing this service receive a refund for the costs from a specially created fund to which all operators using public telecommunications networks contribute. As a result, the

necessarily erodes the profit margin of the entrepreneur and can also cancel it and turn it into a loss, but it is an imposed financial obligation, which draws its foundation from Article 23 of the Constitution, arising from a result that relates to the value of health codified in Article 32. If Article 41 guarantees any entrepreneur, including the medicine manufacturers, a profit margin for a single product, the need for an investigation to establish the costs of individual products, it is possible that - under other constitutional provisions, these profits might in some way be cancelled, eroded, or even turned into imposed forms of consideration and then into losses".

[54] As of 1998, a mechanism for the annual planned pharmaceutical expenditure ceiling has been set up (see Law No. 449/1997), so that in the event of exceeding the maximum spending ceiling borne by the national health service, the deficit is shared between producers and distributors, in particular through the imposition of a proportional reduction in the producers' revenue margin of up to 60% with the remaining 40% coverage of the breakthrough to be borne by the Regions.

costs of the universal service in the sector are proportionally "spread out" among the companies that receive benefits in terms of profits operating in a given market.

Thus, as the firms in the specific sector benefit from operating in that particular market area, they have to bear the financial burden of those parts of the sector's business that are less, or only marginally, profitable. From this point of view, the hypothesis of universal service – even if, strictly speaking, it cannot be considered fully superimposable on that of orphan drugs – can however constitute a useful reminder in analogical terms, because it allows us to confirm that the case examined here is not the only one where the law considers that the companies enjoying the greatest economic benefits in the sector of reference have to bear the costs for activities that are less or only marginally remunerative and that, however, must necessarily be carried out in the pursuit of the constitutional rights of individuals and the good functioning of the overall system.

Returning now to the pharmaceutical sector, it has on several occasions been reiterated that "the additional sacrifice imposed on producers is part of a complex economic manoeuvre that expresses an overall and broader plan intended, on the one hand, to reduce healthcare expenditure and, on the other, to acquire resources to finance it by forfeiting part of the revenues of the players in the drug supply chain, in order to meet the non-reducible need to guarantee essential medicines or medicines for chronic diseases to the widest possible number of citizens without further aggravating the State budget beyond the limits of the financial sustainability of a national economy already in crisis" (Council of State., Sec. III, No. 2686/2014).

In other words, there are requirements that the legislator considers paramount (in the case at hand, the containment of public expenditure and the protection of the health of patients without alternative therapies), for which it is justified to impose compulsory financial obligations[55] on a specific category of

[55] In its Judgment No. 70/1960, the Constitutional Court clarified that "a financial obligation is imposed in accordance with Article 23 of the Constitution when it is established by an act of authority without the consent of the party on which it is imposed, whatever the name given by the law imposing it may be" and can occur not only "when the obligation established by the authority

entities, whose freedom to conduct a business, although constitutionally guaranteed under Article 41 of the Constitution, may be to some extent reduced.

And, in fact, "social goals cannot replace economic calculations as a guiding criterion for business activity, but they do indicate that when there are specific objectives to pursue, and there is a need to protect social needs of equal or greater constitutional importance than market autonomy, the legislator may well intervene with regard to commercial activities, reducing the margin of autonomy of enterprises, thus directing economic activity for social purposes".

Recently, in its Judgment No. 70/2017, the Constitutional Court, called upon to rule on the coverage mechanism for pharmaceutical expenditure for innovative medicines, stated that "the balance between the need to disseminate and promote pharmaceutical innovation and thus protect public health, and that of rationalising and containing healthcare expenditure is achieved by the challenged provision through a reduction in the margins obtainable by companies producing non-innovative medicines protected by a patent", and these companies are called upon to contribute to a system, that of the refundability of medicines supplied under the convention, "from which they themselves derive undoubted benefits".

The Community Courts too (with a judgement of the Court of Justice, Sec. IV, 2 April 2009 in C-352/07) have affirmed that States can issue regulations to regulate the consumption of pharmaceutical products, "safeguarding the financial balance of their health systems" also through the reduction of the sale price of all or only some drugs. In such cases, unlike what has been said for orphan drugs above, the fact that the State receives part of the revenues of pharmaceutical companies does not automatically (and indeed not even on average) translate into a failure (or reduction) in the provision of essential health care to citizens. This, once again, is by virtue of the different characteristics and structures of these markets (competition, profit margins, absolute numbers of patients treated, and the actual impact of annual fluctuations in treatment provided, etc.).

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consists in the payment of a sum of money, but also when the pecuniary sacrifice results from the reduction of a part of the profit otherwise due".

In the conflict between the need to contain public expenditure and free economic initiative, therefore, the latter may be recessionary: it is therefore necessary to verify within which limits this sacrifice is admissible as non-discriminatory and not disproportionate. The question thus arises as to whether, among the various economic operators involved, the manufacturers of non-orphan drugs are the category that can and should actually bear the cost of spending for them. In the pharmaceutical sector, "manufacturers occupy a very peculiar and prominent position, contributing directly and incisively to determine the reduced price of the reimbursable drug and are, therefore, in a position (known as "information asymmetry") of undoubted advantage over other players in the supply chain and, on the other hand, are able to increase the volume of demand through promotion and dissemination" (Council of State, Sec. III, No. 2686/2014).

Compared to the other parties involved (such as wholesalers or pharmacists, and assuming the need not to involve the producers of orphan drugs), the pharmaceutical companies that produce non-orphan drugs hold, in the market of reference, a position of greater advantage, which diversifies them from other operators and makes the sacrifice imposed on them less burdensome. The principle of tax equality implies that "like situations must match like tax regimes, and in the case of different situations there must be a different tax regime" (Constitutional Court July 6, 1972, n. 120). In the case at hand, the different treatment given to manufacturers of non-orphan drugs is justified precisely because of their different position within the market in question.

Moreover, in compliance with the provisions of Article 53 of the Constitution, the solidarity-based ability to contribute justifies drawing more greatly on the wealth of those with greater economic possibilities and "may involve a redistribution of such wealth in favour of subjects who, even within the same economic sector, bear overwhelming burdens and difficulties in any case disproportionate to their current possibilities" (Council of State, Sec. III, No. 2686/2014). The coverage mechanism for the pharmaceutical expenditure for orphan drugs creates, in reality, the effect of a "redistribution of wealth among the elements of the supply chain" (Council of State, Sec. III, No. 2686/2014) and, moreover, respects the ability of the individual company to

contribute, as the share of coverage is determined proportionately to the turnover from the sale of non-orphan drugs[56].

It should also be borne in mind that the burden of covering pharmaceutical expenditure in excess of the state coverage ceiling is not entirely borne by pharmaceutical companies producing non-orphan drugs, since in the case of hospital pharmaceutical expenditure, the burden is shared equally between the pharmaceutical companies and the Regions that have exceeded the regional expenditure[57] ceiling. As for national pharmaceutical expenditure, coverage not only falls to the pharmaceutical companies but also to the distribution chain, namely to wholesalers and pharmacists (in retail sales, the costs are also borne by the companies that produce orphan drugs)[58].

In conclusion, in the words of a ruling by the Council of State, the legislator did not intend to "expropriate the profits of pharmaceutical manufacturers, sacrificing their economic freedom protected by Article 41 of the Constitution, but to impose a modest and temporary levy on profits in such a way as to guarantee both a saving in pharmaceutical sector health expenditure in the pursuit of the public interest - which certainly prevails over the selfish interest asserted by the producers themselves - in the provision of essential levels of pharmaceutical assistance, in the face of the increasingly pressing need to contain public expenditure; and finally, with regard to producers and despite the current extraordinary negative economic circumstances, to generate a reasonable profit margin constituting the inviolable nucleus and the irrepressible goal of private economic initiative".

Having established therefore, that the need to guarantee the protection of the health of those suffering from rare diseases justifies a lessening of private economic freedom and that, in the case at hand, this lessening necessarily involves the category of pharmaceutical companies that produce non-orphan drugs, the question now arises as to whether this mechanism has been undermined in any way by the progressive increase in pharmaceutical expenditure for orphan drugs in recent years. In

[56] On this point see the case law of the Constitutional Court concerning discounts on the price of medicines and, in particular, Judgment No. 102/1993, No. 144/1972, and No. 70/1960.
[57] See Article 15(7) Decree Law No. 95/2012.
[58] See Article 5(3) Decree Law No. 159/2007.

other words, the question arises as to whether the reduction in the rights of the pharmaceutical companies that have to bear the cost of coverage is also justified in terms of the increase in this expenditure.

The question must be addressed from the points of view of two distinct and concurrent terms: the proportionality of the measure and the tolerability of the sacrifice on the part of non-orphan drugs marketing authorisation holders; the absence of the risk of bias (in terms of undue enrichment) in favour of companies holding marketing authorisation for orphan drugs.

As for the first profile, the necessary starting point must be the statistical data available. As already mentioned above, expenditure on orphan drugs grew between 2010 and 2015 from €657 million to €1,393 million, rising from 3.50% to 6.1% of total pharmaceutical expenditure. This growth appears, in absolute terms, far from negligible; what stands out, however, is the share of the actual cost shift borne by the other pharmaceutical companies within the overall cost per pharmaceutical expenditure and payback dynamics. Considering the data (the latest certain figures), for the year 2013 (recording an expenditure of €914mln, equal to 4.65% of the total), the overall data are as follows: a) total pharmaceutical expenditure borne by the State amounting to €16,625.2 mln; b) hospital pharmaceutical expenditure amounting to €4.497 mln; c) an overspend in terms of the ceiling of €773 mln, d) the total share of the coverage borne by marketing authorisation holders amounting to €368 mln (the other half being borne by the Regions, as explained above in §3), and e) the coverage specifically attributable to orphan drugs borne by marketing authorisation holders, amounting to €59mln.

In concrete terms, the cost of coverage for orphan drugs, spread pro quota among all the marketing authorisation holders is therefore 1.3% of their aggregate turnover in relation to hospital pharmaceutical expenditure and just 0.4% of the total turnover for the sale of drugs covered by the national health service. This figure, however, is not yet fully representative of the actual annual turnover of pharmaceutical companies in Italy, which obviously also includes medicines paid for directly by patients.

In the light of these data, the sums levied on pharmaceutical companies (also considering the presumable increase of the estimates in 2013, following the mentioned trend)

still appears to amount to a fraction of their total revenues, both in terms of modalities and quantities, which can be considered quite tolerable from the economic point of view, also considering the profit margins from the average revenues in the pharmaceutical sector. This is without prejudice, therefore, to the "reasonable profit margin" that, in the current economic circumstances, the Council of State considers "the inviolable nucleus and the irrepressible goal of private business". On the contrary, as mentioned above, extending the payback system to orphan drugs would produce a substantial erosion of the revenues and profit margins of manufacturing companies (up to the median value of 12% of the turnover), beyond the thresholds of tolerability and proportionality of the duty discussed so far. It should also be borne in mind that the coverage for in-hospital pharmaceutical expenditure is borne equally by the pharmaceutical companies and Italy's Regions, in a context in which orphan drugs are used mainly in the hospital sector. National legislation therefore hooks the sacrifice required of private individuals to a similar sacrifice borne by the regional budgets in order to ensure the overall sustainability of the measure. Lastly, the amount of duty payable is substantially predictable, as is its evolution over time.

On the whole, this form of levy is not unjustified in the light of the case law of the Constitutional Court on the ability to pay and the corollaries of predictability, reasonableness, congruity, and proportionality. Essentially, the existing coverage system, despite growing pharmaceutical expenditure for orphan drugs, does not seem to call for a disproportionate or intolerable sacrifice on the part of the companies concerned, nor does it conflict with the principles of equality, equal treatment, and respect for the ability to contribute. On the contrary, it seems to include a reasonable balance of conflicting interests: the protection of the health of those suffering from rare illnesses and the containment of public spending.

The problem of the general sustainability, in the medium and long term, of the current mechanisms to cover overspending in the health sector (as a whole) is different and broader, in the context of a prolonged quota system applied to available public resources. Of course, it is likely that, with respect to the current dynamics, the model will have to be rethought in the future; on the basis of the data set out above, however, the share of coverage

arising from overspending for orphan drugs (2013 data) amounts to just 16.1% of the total costs of the coverage for in-hospital pharmaceutical expenditure, a percentage that shrinks even more compared with total pharmaceutical expenditure. It therefore appears difficult, at present, to attribute to the cost of orphan drugs an impact such as to undermine the constitutional adequacy of the payback system as it is currently regulated.

With regard to the second question, relating to risks of overcompensation to the undue benefit of orphan drug marketing authorisation holders, it has been conjectured that this may occur when a drug is improperly termed "orphan" in the absence of any real clinical grounds (constituting a waste for the national health service and super-profits for the pharmaceutical companies). It may also happen when a drug is used outside its own sphere for diseases that are not actually rare (for example, when they contain active ingredients that can be used to treat both rare and common illnesses; or when the orphan drug is developed for a rare sub-population of patients suffering from a common condition but can also be used also to treat all the other patients suffering from that condition).

In practice, however, such risks are averted both upstream and down. Upstream, by means of procedures for the classification of orphan medicinal products (EC Regulation 141/2000 expressly provides for cases of designation for sub-populations, introducing appropriate safeguards; moreover, in the case of designations for rare and non-rare diseases, diverse medicinal products exist, and are accounted for differently). Downstream, they are avoided thanks to mechanisms for monitoring and controlling the use of the drugs themselves (it is, in fact, common knowledge that in most cases, the use of orphan drugs is directly detected in the so-called *AIFA* registers and therefore subject to direct monitoring for each single clinical case treated; moreover, 86% of orphan drugs are authorised for just one type of treatment and a further 11% for two).

At the very least, such risks may be invoked to justify revisions to the authorisation and control procedures but not to call into question a legislative framework whose constitutionality and effectiveness do not appear to be in doubt.

12. Extension of the payback obligation to pharmaceutical companies producing orphan drugs, and possible effects on the right to health of patients suffering from rare diseases

The analysis carried out so far has ascertained the constitutional need for legislation to guarantee preferential treatment for research on - and production of - orphan drugs. At the same, it has confirmed the constitutionality, within the limits of reasonable proportionality, of mechanisms for the partial offload of the costs incurred onto companies operating in the ordinary pharmaceutical sector. It has also shown that the current legal framework, based on negotiated prices for orphan drugs, in the absence of "ceilings" on final expenditure, is a model capable of validly ensuring the need to safeguard the "non-reducible core" of the right to health of patients with rare conditions.

At this point in the analysis, however, it remains to be considered, following the logical-expositive line of thought set out in the introduction, whether there are any other possible regulatory alternatives capable of respecting the constitutional constraints on the subject, likewise able to guarantee the ultimate goal of health protection but offering a different distribution of the economic burden this entails compared with the current system. In other words, the issue is that of the existence of possible forms of sharing and partial reallocation of the sacrifice previously inflicted on pharmaceutical companies and the Regions, including at the expense – under certain circumstances and conditions – of the very companies that produce orphan drugs.

This question is also reasonable in the light of the proposals for reform within the sector, the legislative amendments already proposed (but not yet adopted), and the models applied in apparently similar cases. Serious reflection on the subject, moreover, is also called for by the principles upheld in constitutional case law on the subject of innovative medicines, most recently set out in repeatedly cited sentence No. 70/2015.

Here, the Court considered it constitutional to transfer the overspend on State coverage to the rest of the pharmaceutical companies; nevertheless, it also remarked that this system may also be of temporary duration, with periodic review of the legislation, in virtue, among other things, of a "reduction of the contributions for companies holding marketing authorisation for non-innovative drugs", the "gradual transfer of the burden onto

the companies with marketing authorisation for innovative drugs", and the plurality of "options available to the legislator". For example, if they are contemplated possible corrections to the current system for covering overspend on orphan drugs, we might consider establishing *ad hoc* funding up to an annual maximum figure, which is what happens in the case of innovative drugs, or else fixing annual budget ceilings, established or negotiated per individual orphan drug or manufacturing company.

Beyond the obvious need to evaluate the actual configurations of these hypotheses on a case by case basis, these solutions raise some serious doubts in terms of conceptual approach. First of all, it would appear highly questionable to use the legislative framework for innovative drugs as a parameter of comparison. While it is true that the two categories – innovative drugs and orphan drugs – are comparable in that they impact on and change the consolidated flow of demand for treatment, there are some features that distinguish them: an innovative drug may compete with other drugs for treatment of same condition (thus creating compensation between over - and under-budgeting), unlike an orphan drug that by definition operates in a field not covered by another comparable drug. Innovative drugs are open to potentially vast consumption, whereas that of orphan drugs is extremely limited. Lastly, orphan drugs (with very few exceptions) do not normally guarantee a cure but rather the stabilisation of an illness in its chronic phase: the number of patients treated is therefore inevitably destined to increase.

In concrete terms, considering the current methods of quantifying and allocating the percentages of national health spending allocated to pharmaceutical expenditure, it is difficult to imagine an imposition of ceilings or quotas that would not produce direct negative effects on the production and administration of an orphan drug. The fundamental problem is how to establish the degree of public funding due to (positive or negative) variation in historical expenditure: an approach structurally incompatible with the introduction of new orphan drugs or even, simply, with the extension of existing drugs to new patients. Expenditure on orphan drugs is in fact by definition incremental, so a ceiling based on historical trends could never be respected.

Once the annual expenditure ceiling has been reached, in the absence of market competitors and ruling out a reduction in the number of patients being treated, a random patient will find him/herself bereft of treatment, unless the manufacturing company agrees to deliver the drug anyway and free of charge. Naturally, the health system cannot rely on liberal concessions on the part of the entrepreneurial class, nor (in such cases) can it speculate on the ethical constraint that may have led them to make such concessions.

Practically speaking, the imposition of spending "ceilings" that can also be sustainable for companies producing orphan drugs would presuppose a radical rethinking of the current models of financing health expenditure, with a shift away from the criterion of previous expenditure to techniques for forecasting increases in demand. In other words, "programmatic" spending thresholds must be established, quantifying the foreseeable increase in patients suffering from rare diseases needing treatment, considering their inevitable growth as an effect of the chronicization of existing patients and the onset of new cases. These solutions, apart from the obvious technical difficulties, do not appear realistically feasible.

It is true, from another perspective, that some specific orphan drugs could be identified whose levels of turnover are such as to be able to allow them - in the abstract and from a purely financial point of view - to be subjected to an albeit partial or gradual payback regime. Beyond ethical aspects outlined above, such measures could have a very negative effect on future investment in new orphan drugs, undermining the confidence of the industrial sector in the stability of the current regulatory framework and the economic guarantees it can provide. Moreover, it should be borne in mind that the drugs with the highest sales revenues are also those that ensure the best clinical results and target a wider pool of patients. Imposing a payback obligation on these drugs would therefore discourage other pharmaceutical companies from investing in that sector (affecting the profit differential), and thus prevent the growth of competition in research into the most promising drugs and sectors.

The stability of regulatory framework, on the other hand, appears to be even more important in the light of current production scenario, which is result - as previously described - of

a rigorous selection of companies that have been able to remain on the market and drugs that have been able to reach the stage of final approval and commercialization. In order to assess sustainability of a compulsory levy on proceeds of individual orphan drugs on the market today, the dissuasive effect on the entry of new operators in this market and the launch of new trials cannot be ignored.

The same consideration also holds for an additional possible alternative solution: the "payment at results" mechanism, in other words a payment conditional on the successful efficacy of the orphan drug on the single patient suffering for a rare disease. This mechanism could be effective for innovative drugs: the aim of these drugs is improving the condition of the patient compared to drugs that are already on the market. Therefore, it is expected that innovative drugs are better than the previous ones. Considering that the number of patients targeted by the innovative drug is not limited, pharmaceutical companies are encouraged by the market to develop such drugs.

However, for orphan drugs for the treatment of rare diseases the situation is different. These drugs are intended to treat a limited number of patients and, usually, in the absence of any previous treatment for the disease. We have already described the system of incentives aimed at covering research and development costs and the strict rules for marketing authorization. The "payment at results" mechanism would be a strong disincentive to pharmaceutical companies' investments in the sector. On the contrary, it is necessary to work at the removal of the distortions reported in the first part of this article. But, if anything, we need to improve effective and proper controls and develop rules in order to prevent distortive effects.