OSSFOR
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JOINT VENTURE BY CREA Sanità & OSSERVATORIOMALATTIERARE

EXECUTIVE SUMMARY OF I° REPORT OF OSSFOR 2017

"IMPACT AND GOVERNANCE OF RARE DISEASES AND ORPHAN DRUGS"

ORPHAN DRUGS OBSERVATORY

OSSFOR is the first think-tank devoted entirely to the development of policies for governance and sustainability in the field of rare diseases. Born in 2016 as a joint initiative of the research center C.R.E.A. Sanità (Consorzio per la Ricerca Economica Applicata in Sanità - Consortium for Research in Economics Applied to Health) and the Osservatorio Malattie Rare (Observatory for Rare Diseases) OMAR, with the aim to systematize the existing information, fill the gap of knowledge and information about the field, encourage an open and direct confrontation between institutions and key stakeholders. The goal of OSSFOR is to contribute towards ensuring quick access to treatment and care for rare disease, encouraging synergy between the institutional, political, academic and business sectors, through a useful open discussion to identify the best strategies to be implemented. To this end, it plays an ongoing role of research and monitoring that results in an Annual Report.

The OSSFOR is funded by an annual and unconditional support of the greatest number of companies engaged in research and development of orphan drugs. The extreme "fragmentation" of lenders is a maximum guarantee of independence and impartiality with respect to lenders themselves and towards institutions.

The publications of OSSFOR - reports, handbooks, analysis, background papers, organizational and regulatory proposals and any other document drawn - are made public through the publication on the site www.osservatoriofarmaciorfani.it

KEY POLICY MESSAGES

1. In-depth knowledge of the epidemiology and the needs of rare disease patients must become a priority of health policies in order to anticipate the needs and govern the system.
2.The efficiency and effectiveness of orphan drugs and other related technologies must be strictly proved, but patients should have quick access to therapy to limit the health and human costs of a late treatment.
3.The technologies must be evaluated ensuring efficiency of intervention, their sustainability and equity of access.
4.The use of orphan drugs and other technologies needs to be optimized in order to maximize the return in terms of health, coordinating treatment within an overal managementl process, taking into account all the social and health needs of the patient.
5.National and regional policies must work to ensure that healthcare organizations can support the economic impact of rare diseases, independently from all diverse prevalence at local and regional level.

OSSFOR ACTIVITIES ARE MADE POSSIBLE BY THE NON-CONDITIONAL SUPPORT OF:

EXECUTIVE SUMMARY

PREMISE

The Orphan Drugs Osservatory (OSSFOR) is the first research center and think tank dedicated to developing policies for governance and sustainability in the field of rare diseases. Born in 2016 by a joint initiative of the Research Center C.R.E.A. Sanità (Research Consortium for Applied Economics in Healthcare) and the journal Osservatory of Rare Diseases OMAR with the aim of systematizing existing information, filling the gap in knowledge and information on the sector, facilitating an open and direct confrontation between institutions and key stakeholders.

The goal of OSSFOR is to help ensure rapid access to therapies and assistance to rare patients by promoting synergies between the institutional, political, academic and business worlds through a free exchange in order to identify the best strategies to be implemented.

Among its objectives OSSFOR is to publish annually a Report on the dissemination of the evolution of knowledge related to an economic and social impact and to monitor the evolution of health policies, regulation and management of rare diseases and their technologies, primarily orphan drugs.

This report is divided into 4 parts: the first analyzes the regulatory aspects of the rare diseases sector and orphan drugs; the second part is devoted to the analysis of "demand"; thirdly, then analyzes the supply in terms of technology; fourthly, a focus on governance in the industry.

The first report focused essentially on three aspects: the first, a preliminary to the rational formulation of any hypothesis of intervention, concerns the knowledge of the rare disease phenomenon, both in terms of epidemiological and economic impact on the health service; the second aspect is the regulatory one, which observes in the sector peculiarities that require a thorough study; the third aspect is the technology for rare diseases, and in particular of orphan drugs, which is at the heart of both welfare and industrial policies: in-depth analysis is obviously appropriate in the light of the

complexity of the sector and the impact of innovation on patients' opportunities and quality of life.

Obviously, with the project having a multi-year approach, the various aspects mentioned will be the subject of integration, in-depth analysis and updating in subsequent editions, having to consider this first edition as an initial attempt to systematize the materials.

We also note that the aspects mentioned are characterized by a close interrelation, so that they are dealt with accordingly under different aspects in several chapters of the Report.

SUMMARY OF I REPORT 2017

The Report consists of four parts: the first chapter, dedicated to the Regulatory, describes the Italian and European regulations and Early Access Programs; the second chapter, dedicated to the Demand, contains an epidemiological analysis of patients with rare disease; the third chapter, dedicated to the Supply, examines the processes of the authorization path of orphan drugs; The fourth chapter, dedicated to Governance, contains an analysis of direct health costs and decision making processes for rare disease technologies. In conclusion, a contribution made by EURORDIS that offers a European perspective on access to therapies.

Below is a summary of the main evidence contained in the Report, referring to the full reading for their in-depth study.

We begin with the observation that on the basis of an original survey conducted on the administrative databases of the Lombardy Region and the Puglia Region, the prevalence of rare disease patients, who are recognized with exemption by the NHS can now be estimated in the range 0.46% -0.53% of the resident population, with a significant gender difference: 0.53% -0.55% for females and 0.39% -0.51% for males.

By extrapolating the data, it can be assumed that rare diseases in Italy are within range 270.027-322.763. For exempt patients, the NHS supports an average annual per capita spending in the range of € 4.217-5.003, including contracted pharmaceuticals and in File F, diagnostics, laboratory analysis, visits, ordinary and daytime hospitalizations. Housing and home care are not considered for the scarcity of information, but being still underdeveloped, the expectation is that it has a marginal impact for now.
Even in this case by extrapolating the data, the overall expenditure incurred by the NHS would amount to € 1.35 billion. equal to 1.2% of total public expenditure.
Consider that the underlying data underestimates the phenomena analyzed, mainly because only the patients to whom the SSN recognizes an exemption are considered; however, we observe that while on the epidemiological side the underestimation is certainly relevant (consider that EMA estimates describe 6 -8% of the EU population) on the economic side it is much less, as the exemption is linked to the relevance of absorbing resources. From a financial point of view, however, the burden of the care provided directly by the patients and their care providers is excluded, which we know is certainly significant.

With the caveats expressed, it can be seen how the share of spending on rare patients on average does not differ significantly from that of chronic patients with two co-morbidity.
Entering in more detail, we can point out that age distribution of subjects with rare disease returns a peak of prevalence in adolescent age (10-19 years) and another in the fifth decade (40-49 years).
Ultra rare conditions, however, are more concentrated in younger ages and show a different epidemiological trend than the universal.
Analyzing the sub-population of ultra-rare patients, it emerges that they represent the true challenge in organizational terms: while they amount to between 15.9% and 16.5%

of the universe of rare disease patients, they are divided into over 215 illnesses or groups that access the exemption.

In addition, the complexity is heightened by the fact that variability in the concentration of subjects between the various local health agenzies appears extremely significant, reaching a variation between the one with the highest prevalence and the one with the lowest prevalence of 100%.

The data reverberates on the aspect of economic impact: at least in Lombardy, the average expenditure for ultra-rare patients is significantly higher than the average, with a variation between the one with the highest per capita spending and the lowest of 220%.

Observing, by arbitrary definition, "high cost" patients with average annual expenditure per capita greater than € 50,000, are equal to 0.5% of the rare patients in the Lombardy Region and 0.005% of the Apulia Region , absorbing 11.1% and 0.3% respectively of the total resources; the difference should be analized more profoundly and may concern access barriers, mobility phenomena, but also the result of pure casualty; evidently, since the population Apulia is 50% of Lombardy, it goes without saying that the variability of the estimates is greater.

This concentration shows that there is evidence of a high level of financial risks, which should cause reflection on the current funding system for healthcare providers, which in some regions provide us with ad hoc corrections for high-paying patients, with the risk of generating barriers to accessing essential services.

The analysis, conducted in two populous regions, one northern and one southern, highlights regularity: for example, the predominant cost items are

as were expected, those for pharmaceutical assistance (over 60% of the total cost) and for admissions (about 20% of the total cost).

The average annual per capita expenditure of rare patients is higher at the time of the

certification of the exemption, it is reduced in adulthood and then increased again in the elderly when other pathologies or presumably other health problems concur with the disease.

The resources absorbed by the male gender are far greater than those absorbed by the female (over 60%), despite the epidemiology having an "inverse sign".

Regarding regulatory aspects, reference has been made to European and national regulations, starting from the year 2000, when the European Institutions issued the first Regulation, No. 141/2000, setting rules for the assignment of the status of orphan drugs. In particular, it sought to explore topics such as the requirements for the designation of orphan drugs and the related procedure, and the centralized authorization procedure governed by Regulation (EC) No. 726/2004, mandatory for certain types of drugs, including orphan drugs.
From the analysis of the regulations, the intention of the European Institutions is to encourage the development and production of orphan drugs in order to respond to a series of unmet medical needs. In 2017, the European Medicines Agency authorized, altogether, 73 new drugs, of which 10 with orphan designation.
This same objective appears to be pursued by the nation's legislature, which firstly by Law No. 95/2012 and then with Law No. 189/2012 (subsequently amended by Law No. 98/2013), contributed to the development and production of orphan drugs by granting sponsors the possibility to apply for price / redemption even before the release of the marketing authorization by the European Commission, excluding orphan drugs from pay-back, and finally with the anticipation of a fast-track authorization for orphan drugs and those of exceptional therapeutic relevance.

Further regulation subject to analysis is that related to c.d. Early Access Programs, i.e. those programs aimed at patients with rare, serious or highly disabling illnesses, designed to ensure early access to the medication prior to the marketing authorization

or during the testing phase, if there is no valid therapeutic alternative. In this regard, reference is made to Law No. 648/1996, the Ministerial Decree of 8 May 2003 and Law No. 326/2003. With specific reference to rare diseases, the number of medicines for their care included in the list set up under Article 1 648/96 is 28.
The study of the legislation in question has highlighted the special attention that our country addresses to patients suffering, among other things, from rare diseases, providing them with a multitude of tools characterized by peculiar requirements in order to guarantee their health needs not always satisfied.

Consider that European and Italian legislation have been oriented in recent years, always with a view to ensuring rapid access to therapeutic opportunities for rare diseases, reducing the time of administrative procedures for the marketing of orphan drugs.

To monitor the issue, OSSFOR has conducted an in-depth analysis of market access processes, both internationally and nationally, by building its own database, which will be updated annually.

The first evidence gathered suggests that the time between the designation of orphan drug and the authorization request has increased at a European level through a central EMEA procedure: 34 months (median value 31) for EMEA-authorized medicines between 2003 and 2004, at 74 months (median value 77), between 2015 and 2016.
This increase is associated with a reduction in the duration of the EMA authorization process, thus highlighting how the first phenomenon is the effect of an increasingly early "designation".
Even at the national level (AIFA), there has been a tendency in the last few years to reduce the length of the process: between EMA authorization and price and redemption, in fact, it goes from 29 months (median value 26) to the three-year period 2011/2013 to 13 months (median 12) in the three-year period 2014/2016.

Times are further reduced if the drugs included in the list of L. 648/96 and those in Cnn Class are excluded: for 27 months (median value 26) in the three-year period 2011/2013 at 10 months (average and median value) over the three-year period 2014/2016.

The reduction appears to be related to regulatory developments and, in particular, with the approval of LN 189/2012 ("Balduzzi Decree") and Law 98/2013, which ultimately reduced the time allowed for the conclusion of the negotiating procedure in 100 days from the date of submission of the application.

The "internal" process, i.e. the time for evaluation/negotiation of the AIFA Commission also shows a trend reversal over the period considered, ranging from 218 days (206 median) to 2012/2014 to 197 days (165 median) in the three-year period 2015/2017.

While remaining in the field of orphan drugs, for which OSSFOR has also provided a database for the monitoring of market developments, we note that spending between 2015 and 2016 (for 74 drugs out of 86 monitored on the Italian market) increased by € 244 mil. or 22%, as well as the quantities sold, ranging from 22.4 million minimum fractional units (UMF) to 25.8, an increase of 16%.

Increases in spending and quantities sold are, however, linked to the market access of new drugs and their natural uptake: it is interesting to note that the drugs marketed for the first time since 2013 show a 132% increase in expenditure and in quantity of 70%, while for the previous ones, the increase in spending is about 10% and that in quantity of 5%.

The cost for UMF, therefore, grows by 35% for newly marketed medicines, while it stops at 7% approx. for those "older" ones.

Orphan drug spending on total public and private pharmaceutical spending, while remaining limited, grew significantly in the two-year period considered: in percentage terms, it went from 3.9% to 4.6% (5.0% and 5,9% respectively considering only public pharmaceutical expenditure).

Such an increase in the incidence of orphan drug expenditure on public pharmaceutical expenditure appears, of course, as an increase in therapeutic opportunities, a positive element; patients have found greater responses to their needs and companies seem to be investing in this area despite the difficulties associated with “small numbers”.

The issue of economic impact leads "naturally" to the aspect of redemption and pricing processes.

Examining existing literature shows how the share of charges for orphan drugs tends to settle at 5% internationally (Schey et al.).

The annual cost of orphan drug therapy (in 7 European countries including Italy) varies from just over € 750 to over € 1,000, with an average cost of € 10,000 and a median cost of around € 39,000 (Medic et al).

In terms of Vegter efficacy finds that 57% of the drugs analyzed had a cost per QALY (quality-adjusted life year) gained below the threshold of £ 30,000; more recently, Picavet et al found an incremental cost for QALY gained about € 40,000, varying (approximately) in the range of € 6,000-1,000,000.

According to this study, although the authors have been able to collect pharmaceutical-economic evidence for only 19 drugs, most of them meet the commonly-accepted cost-effectiveness requirements: for about 50%, the cost per QALY is less than £ 30,000 and per 80% to € 80,000.

The key element therefore remains the variability of the results, but it must be contextualized. In other words, the ratio of incremental cost to QALY gained higher and lower, according to the study quoted is 167 times, which may appear in fact inexplicable but which is, however, closely linked to the variability of the prevalence of rare conditions: Among the prevalence of a rare disease at the upper limit of the threshold and an ultra rare disease the ratio is, in fact, 25 times.

Medic's recent work demonstrates the existence of a statistically significant inverse correlation between the cost of years of treatment and the prevalence of rare diseases to which 120 orphan drugs are marketed in 7 European countries (France, Germany, Italy, Norway, United Kingdom, Spain and Sweden).

And correlations, in all countries considered, are even more common for ultra rare diseases.

In other words, there is a clear evidence of the relationship between prevalence and price /cost, and this is easily justified by the fact that the decline in prevalence, and therefore of eligible patients, generally has to increase the price / cost to maintain a constant profitability.

By focusing on Italy, we note that it has a number of orphan drugs considered second only to the UK, with the lowest median annual treatment costs among the countries considered, as well as the lowest average costs, excluding that of Sweden (whose data however can not be considered completely comparable).

Ultimately, it is confirmed that the Regulatory Agencies seem to recognize and manage in a relatively homogeneous and rational manner the issues of profitability, and therefore incentives for investment in the field of rare diseases / orphan drugs; and, for Italy, Messori et al attempted to estimate the relationship between treatment costs and prevalence on the Italian market, thus explaining the "negotiation rule" implicitly adopted by AIFA.

According to this study, for a disease with a prevalence of 2 cases per 10,000, the annual cost of treatment, considered implicitly acceptable by AIFA, would be € 10,000, would go up to approximately € 26,500 for a prevalence of 0.2 cases on 10,000 (ultra-rare) and would be about € 2,000,000 for a pathology with 10 cases in Italy.

It should be noted that the potential turnover in the three mentioned cases varies from € 120m. (prevalence of 2 out of 10,000), € 32 mil. (prevalence of 0.2 to 10.000), and € 20mil. (prevalence of 10 cases in Italy).

It goes without saying that although the "price / cost" progressiveness may seem enormous, as does the cost per single patient, it is widely assumed that profitability for illnesses remains lower and very low, to the extent that it is not profitable.

In conclusion, despite the increasing interests in the sector in recent years, the equilibrium of the sector remains "fragile": this fragility is primarily due to the strong

variability in prevalence, generating risk concentrations with a potentially strong organizational and economic impact for healthcare agencies.

The variability of prevalence, also explains the significant deviations from the cost-effectiveness principle for technology, and in spite of this, remains fragile even from an industrial point of view, although the incentives put in place in recent years have proved effective.

Access times have also improved, although market access processes still require significant times. Ultimately, the real peculiarities in terms of health policies remain the concentration of very high resources on very small groups of people, which can, and in fact, provoke conflicting reactions.

To this, which is a social problem, one can respond with the indications in the document of the National Committee for Bioethics of 25 November 2011 "Orphan Drugs for People with Rare Diseases": *"... a patient suffering from a rare disease is first of all a person who has the right to health care: in this case, he is entitled to obtain proven efficacy, but also as a right to hope for the development of new treatments, thanks to advances in pharmacological research. "*... because ..." *the possession of the best state of health that one is capable of achieving constitutes a fundamental right of every human being "and given that" ... the criterion of efficiency such as that based on the cost / effectiveness of the interventions, effective distribution of resources with a view to purchasing as much public health as possible, does not promise to ensure enough namely the individual rights and the needs of 'marginal' patients, it will be necessary to identify additional or alternative policy tools that can satisfy them. In fact, the primary goal (ideal) to be achieved is to improve the condition and quality of life of each patient, without discrimination based on the nature of the disease or the cost of therapy. "*

Consorzio per la Ricerca Economica Applicata in Sanità

C.R.E.A. Sanità (Consortium for Research in Economics Applied to Healthcare) is a nonprofit Consortium, promoted by the University of Rome Tor Vergata and the FIMMG (Italian Medical Association of General Medicine). The Consortium was born in July 2013, gathering the twenty years experience and skills of a multidisciplinary team of coordinated researchers, at the University of Tor Vergata, by Prof. Federico Spandonaro, currently President of the Consortium Team who has become a point of excellence for economics and organizational research in the health field.

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The OMAR Observatory of Rare Disease is the only journal in Italy and Europe focused solely on the issue of rare diseases and orphan drugs and with full free access. Born in 2010, in seven years it has built close relationships of information exchange and collaboration with the world of patient associations, institutions, medical practitioners and active researchers in the field and pharmaceutical companies engaged in the sector of orphan drugs.
The portal has obtained the Hon Code certification for medical information reliability.
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