OSSFOR
OSSERVATORIOFARMACIORFANI
JOINT VENTURE BY CREA Sanità & OSSERVATORIOMALATTIERARE

HANDBOOK OF OSSFOR

No. 1 - THE REGULATION OF RARE DISEASES AND ORPHAN DRUGS

HANDBOOK OF OSSFOR

The world of Rare Diseases and Orphan Drugs has been for few years in the middle of a wave of interest, both from the public face and the private, which has allowed for an increasing number of analyzes and studies. This wide availability of information, if organized in a shared model, can promote inter-institutional dialogue aimed at defining useful policy towards the effective governance of the sector.

The Osservatorio Farmaci Orfani (Observatory Orphan Drugs) OSSFOR, founded by the Centre of Health Research CREA (Consorzio per la Ricerca Economica Applicata in Sanità -Consortium for Research in Economics Applied to Health) and by Osservatorio Malattie Rare (Observatory for Rare Diseases) OMAR, has among its objectives to systematize the existing information and fill in the gaps information on Rare Diseases and Orphan drugs. The result of this activity is the periodic production of *I OSSFOR HANDBOOK* that deal with in-depth single issues, topics useful to provide a more comprehensive picture of the world of rare diseases and orphan drugs.

The contents of The OSSFOR Handbook can be used, with permission, from all who carry out their activities in the field of rare diseases and orphan drugs and circulated on the occasion of any public or private meeting.

The Handbook I, entitled *"The Regulation of Rare Diseases and Orphan drugs"*, is a collection of all the regulations governing the sector, accompanied by some information to help provide a more extensive overview of the field. The publication focuses on a series of definitions, identified at European and national regulatory level, to frame clearly and precisely what is meant by rare disease and orphan drug. Its purpose is to enclose in one document, all information in the field accompanied by normative references in order to indicate a certain and clear as possible reference standard.

CONTENTS OF THE HANDBOOK OSSFOR WERE EDITED BY:

Stefania Collet, Osservatorio Malattie Rare
Francesco Macchia, Osservatorio Farmaci Orfani
Barbara Polistena, C.R.E.A. Sanità
Federico Spandonaro, C.R.E.A. Sanità
Roberta Venturi, Osservatorio Farmaci Orfani

OSSERVATORIO FARMACI ORFANI (ORPHAN DRUGS OBSERVATORY) OSSFOR

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:

AMGEN · Amicus Therapeutics · Biogen · BIOMARIN · Celgene 2016 Dieci anni in Italia.
Chiesi People and Ideas for Innovation in healthcare · CSL Behring Biotherapies for Life™ · Dompé · Intercept · ORPHAN EUROPE RECORDATI GROUP
SANOFI GENZYME · Shire · Takeda · VERTEX THE SCIENCE of POSSIBILITY

INDEX

"ORPHAN DRUGS FOR PEOPLE SUFFERING FROM RARE DISEASES"

Extract from the National Committee document on Bioethics of 25 November, 2011

When it comes to rare diseases the reference is to a wide and heterogeneous group of diseases characterized by a low frequency in the population, whose classification criterion is usually purely epidemiological. Diseases that are little known and poorly studied, which often have a chronic course and a disabling outcome, and / or premature mortality, and considering only the European population, affecting a whole of about 30 million people, half of whom develop the disease already in childhood. As regards the scope of the term rare disease, in the European context, "the rare disease entity is configured with a social health character, including not only the diagnostic and therapeutic aspects, but also those inherent in the prevention, rehabilitation and social-economic support."

It should be noted, however, that despite the growing awareness in recent years towards the issue of orphan diseases, their lack of individual epidemiological importance makes them still unattractive for the industry, without incentive to research and develop remedies that would not find a market adequately profitable. On the other hand, when they are available, these treatments are very expensive, while not being, in most cases, sufficiently documented in effectiveness and safety. For these reasons interventions of orphan drugs are often less efficient than those simpler and cheaper, secure - even if sometimes limited -, effective, that apply to larger populations of patients.

The National Committee on Bioethics believes, however, that the latter consideration, mainly based on the criterion of cost-effectiveness and aimed at protecting public health, can not and should not be separated from specific attention for the condition of suffering of people affected by rare diseases and solidary efforts for the promotion of their health.

The patient suffering from a rare disease is first and foremost a person who has the right to health care: a right which, in this case, is expressed as a right to receive proven treatments, as well as a right to hope in the development of possible new treatments thanks to advances in drug discovery. The two rights seem implicit in the preamble of the constitution of the World Health Organization (WHO), which states that "the possession of a state of better health that is able to be achieved is a fundamental right of every human being."

Rare diseases raise numerous problems, both for the person who is affected, often burdened with severe or very serious disabilities, both for his family and for the community.

Individual and family problems mainly concern:

- *the difficulty or the impossibility of access to correct diagnosis - due to the failure to find a reference center specialized in the clinical pathology in question - with the consequent psychological burden and deterioration of the status of health of the patient*
- *delay in diagnosis that adversely affects prognosis*
- *isolation and the lack of scientific knowledge and information about both the disease and on existing laws and rights*
- *the lack of appropriate medical care and rehabilitation and psychological therapies necessary, taking into account the chronic and disabling nature of the majority of rare diseases and the disruption and destabilization that the experience of the disease brings to the patient and the family*
- *the difficulty of access to treatment and care, both with regard to the access-availability of innovative medicines, high or very high cost, specific for a given rare disease, and already on the market in Europe and, when there are no specific etiological treatment, nor access to other possible treatments*
- *strong inequalities at the regional and local levels with regards to access, to diagnosis, to innovative therapies and, more generally, to health care and social services*
- *the high costs of treatment, taken as a whole, and lack of support measures that meet the needs of daily and ongoing assistance determined by the pathology, whose burden falls almost entirely on the nuclear family unit, causing it impoverishment and often estrangement from the world of work*

- *precarious conditions, frequently perceived as serious or very serious by people suffering, even after getting the diagnosis*
- *the serious social consequences for the patient (stigmatization, isolation at school and in work activities, difficulty in developing a network of social relations).*

The number of these diseases is very high (at least 6000 according to WHO). As a result, the total number of patients suffering from rare diseases is huge: an estimated 30 million in Europe, of which more than 1 million in Italy (although the lack of comprehensive data on the population of the rare patients makes it difficult to estimate precisely), 25 million in the US.

Two issues of great relevance to the decisions about resources to be allocated for the treatment of rare diseases, are the effectiveness and efficiency of intervention and the possibility of their measurement. The QALY (Quality-Adjusted Life-Year) is the most widely used instrument for determining the value of a drug. The QALY measures the survival and quality of life of patients in reference to a treatment. The cost of treatment, in relation to the QALY, is, in general, a measure of cost-effectiveness to establish the convenience of an intervention to another.

In a system with defined financial resources (every year a budget for health spending is set, with percentage as the ceiling on pharmaceutical expenditure), the cost per QALY would, in the future, be the instrument through which actions are prioritised: as part of the planned expenditures the most effective interventions would be reimbursed. More public health would be achieved with the available budget.

The criterion of the QALY, however, is not without critical considerations, in general, and in particular when it comes to rare diseases. It has a purely statistical value, which leads to a single social factor in the evaluation of a health intervention spread across multiple subjects, based on an overall calculation that does not take into account the different conditions of the persons concerned. It should be emphasized that the QALY should not be of clinical medical reference, as it is a tool for resource allocation. Its application, as an exclusive criterion, will, therefore, not meet the requirements of fairness in the allocation of scarce resources to a question of mere efficiency.

If a criterion of efficiency as one based on the cost / effectiveness of interventions, while ensuring an efficient allocation of resources in view of the purchase of the greatest possible amount of public health, does not promise to sufficiently secure individual rights and needs of 'marginal patients ', it will be necessary to identify policy instruments, additional or alternative, that can meet them. The primary goal (ideal) outcome must be, in fact, improved conditions and each patient's quality of life, without discrimination as to the nature of the disease or the treatment costs. Towards this goal should be addressed all the energy of researchers, health professionals and those who manage public health, supported by the same patient organizations. The National Committee of Bioethics therefore maintains its reflection open to the contributions of new evaluation criteria.

The right to health care of people with rare diseases can not be questioned by the contraction of economic resources and allocation choices of funds guided by the sole criterion of cost-effectiveness. However, aware of the financial commitment required by research and therapy in the field of rare diseases and the difficulty that this commitment creates in the choice of priorities that guarantee the right to health of all, the National Committee of Bioethics suggests the adoption of some measures capable of limiting the burden. These are general measures and guidelines of principles, which do not allow us to propose concrete solutions, specific and immediate, but outline the reference values of health policy choices in this area. These measures include in summary:

1. *the recommendation to European and national legislators to adopt a new definition of a rare disease, based on more stringent epidemiological criteria, and to establish a revenue ceiling above which revoke the orphan drug designation and its advantages and incentives, in order to discourage speculative policies based on the extent of clinical indications of very expensive products;*

2. *the promotion of management and treatment, pharmacological and non-pharmacological, of rare diseases, hereditary or not, also reducing the number of undiagnosed cases, reducing the time of diagnosis and increasing the availability of genetic counseling for hereditary diseases;*
3. *the promotion of clinical trials on a multicenter, national and international basis, in full respect of the persons whom experiments are performed (children and other particularly vulnerable conditions) and ethical criteria (informed consent, confidentiality of information, etc.); for this purpose it is desired the realization of a European fund for the translational research of new orphan drugs;*
4. *promotion of transfer of research results in the treatment of rare diseases and the simultaneous adoption of a greater rigour in the criteria for evaluating the innovation of orphans drugs before they are placed on the market, ensuring the best national and international clinical practices for all patients, without exception or regional differences;*
5. *monitoring the efficacy and tolerability of drugs granted for compassionate use or used in off-label form;*
6. *the recovery of resources in order to sustain the burden of orphan treatments through the redistribution of the expense for some classes of drugs, widely used and low cost, by the NHS to patients, but also by promoting campaigns to ensure that large companies, whether pharmaceutical or producers of consumer goods, are encouraged to 'adopt' one or the other of orphan diseases, considering that 'ethics' of a product, once advertised, can be an added value.*

RARE DISEASES

A disease is defined as rare when its prevalence, ie the number of cases in a given time in a given population, conventionally does not exceed a certain threshold.

In the European Union (EU) (European Program of Action On Rare Diseases 1999-2003) this threshold is fixed at 0.05% of the population, or 1 in 2,000 people, or 5 per 10,000.

Italy adheres to the European definition. Other countries adopt slightly different parameters: for example, in the Uinted States a disease is considered rare when it does not exceed the prevalence of 0.08% threshold; Japanese law, however, defines a rare disease that includes less than 50,000 cases (4 cases per 10,000).

The low prevalence does not mean that people with rare diseases are few. It is estimated that the phenomenon affects millions of people in Italy and tens of millions throughout Europe.

Moreover, the number of rare diseases known and diagnosed is between 7,000 and 8,000, but it is a figure that grows with the progress of science and, in particular, with advances in genetic research.

Many pathologies arrive at just a prevalence of 0.001%, ie 1 case per 100,000.

Currently there are several lists of rare diseases, such as

- the National Organization for Rare Disorders(NORD)
- Office of Rare Diseases
- Orphanet

In Italy the National Institute of Health, on the advice of the Ministry of Health, identified with the Ministerial Decree 279/2001 (the Regulation of the establishment of the rare disease national network and exemption from participation in the cost of related health services), a rare disease list for exemption from costs sharing (see. below).

NORMATIVE FRAMEWORK
REGULATION (EC) No 141/2000 on Orphan Medicinal products. *Point No. 5 of the Preamble.* *Pathology with spread no more than 5 cases per 10,000 individuals is generally regarded as the appropriate threshold.* ***REGULATION (EU) No 536/2014, on clinical trials on medicinal products for human use.*** *Point No. 9 of the premises.* *Serious diseases, debilitating and often life-threatening affecting no more than one person in 50,000 Union.*

NATIONAL PLAN FOR RARE DISEASES

The National Plan for Rare Diseases approved in the State-Regions Conference on 16/10/2014, was enacted in order to give unity to the actions undertaken for rare diseases and to respond to the need to share the same strategy with all role players in the field.

The plan responds to the EU Recommendation 2009 / C 151/02, with which the Commission and the Council of Europe have indicated to member states the need to adopt a national plan for rare diseases by 2013.
The National Plan for Rare Diseases, after a premise and an introduction relative to the national and European contexts, is dedicated to analyzing the most critical aspects of care, focusing on the organization of the network of departments, on the monitoring system (national register and regional registers), on problems related to the encoding of rare diseases and databases, but especially on the diagnostic and care pathway, as well as tools for therapeutic innovation (including orphan drugs) and the role of associations.

Undoubtedly, training and professional development of health workers, to ensure thorough transfer of knowledge, are believed to be important elements in the field of rare diseases; The Plan emphasizes the importance of this topic and also looks at the value of information, not only for health professionals, but also for the sick and for their families.
Specific attention is then reserved for the prevention and early diagnosis, because one of the main difficulties encountered by people affected by a rare disease is to obtain a timely diagnosis of the disease and receive appropriate treatment in the initial phase, when it is still possible to determine a significant improvement in the quality of their lives.

A key chapter of National Plan for Rare Diseases is dedicated to the Centers of Expertise. In view of the limited number of patients and limited available experiences, in order to ensure the diagnosis and treatment of these diseases, the EU considers indispensable the establishment of a European reference network for rare diseases, in which privileges, when appropriate, the transfer and exchange of experiences, the exchange of information and data, biological samples, of radiological images and other diagnostic elements, instead of moving the patients.

At the European level, the European Union Committee of Experts on Rare Diseases (EUCERD) has issued several recommendations on Centers of Expertise, on the establishment of European reference networks, on registers, on indicators for national plans and the added value of orphans medicines.
In the field of networking and identification of structures that are part of the same, fundamental documents are the Recommendations on Quality Criteria for Centers of Expertise for Rare Diseases in the Member States of 24 October 2011 and the Recommendations on Rare diseases European Reference Networks (RD ERNS) of 31 January 2013.

According to the Recommendations of 2011, the Centers of Expertise for rare diseases are recognized by Member States as "expert" facilities for diagnosis and treatment of patients with rare diseases in a defined geographical area, preferably national and, where necessary, international. They include or coordinate multidisciplinary skills, contribute to developing diagnostic and therapeutic protocols, guidelines and best clinical practices, and are connected with specialized laboratories and other facilities (eg rehabilitation), participate in scientific research activities, contribute to the formation of doctors, paramedics and non-medical professionals, provide information and collaborate with patient organizations. The selection criteria of the Centers of Expertise are contained in the Plan.

Another key point is the establishment of European Reference Networks (ERNS) for diseases or groups, resulting in the determination of expert centers nationwide, identified by Member States according to the specific situations of the different countries / regions.

According to the European Community approach, it is up to Member States in the territory of competence the task of identifying the experiences to be made available, defining quality indicators to be shared with other Member States and provide appropriate information to professionals and healthcare providers, citizens and to patient organizations, with regard to conditions of access to the structures of ERNS.

At European level the types of services are defined and the necessary facilities and resources to be shared and formally identified, how to share the skills and information, including information on best practices to be disseminated to aid diagnosis and proper treatment.

NORMATIVE FRAMEWORK
PRESIDENCY OF THE COUNCIL OF MINISTERS *Permanent Conference for relations between the state, the regions and the autonomous provinces of Trento and Bolzano, Repertoire acts n. 140 / CRS of 16 October, 2014* *...., We should approve the "National Plan for Rare Diseases".*

EXEMPTION CRITERIA FOR RARE DISEASES

The Ministerial Decree n. 279/2001 established under what conditions people with rare diseases are entitled to exemption from sharing in the costs of services provided by the National Health Service.
The criteria entitling to the specific exemption are contained in Legislative Decree 124/1998 and include:

- the rarity (referred to the prevalence limit <5 / 10,000 inhabitants established at European level)
- to the clinical severity
- to the degree of invalidity
- the onerousness share of participation (deriving from the cost of its treatment).

It takes into account, then, two more specific criteria: the difficulty in making the diagnosis and the difficulty of identifying the proper treatment to often complex care needs.
The list of rare diseases exempt from sharing has recently been extended by Decree of the President of the Council of Ministers of January 12, 2017 the new definition of levels essential for assistance (LEA). The list currently includes 583 diseases, but some regions have approved exemptions for more diseases than those provided by Decree 279/2001.
Lists of LEA related to chronic diseases, MR, vaccines and hospital services whose cost is covered by the state have been updated in 2017... With the definitive introduction of the new LEA the list of rare diseases has been rewritten, with the addition of 110 new diseases.

The exemption is granted on

- all appropriate and effective services for the treatment and monitoring of rare disease ascertained and for the prevention of further aggravation
- interventions for the diagnosis, carried out by the deparments of the national network, based on a suspected diagnosis formulated by an NHS specialist
- genetic investigation of the assisted family may be necessary to diagnose a rare disease of genetic origin for the patient.

NORMATIVE FRAMEWORK

DECREE 18 May, 2001, No. 279
Regulation of the establishment of the national network of rare diseases and exemption from participation in the cost of related health services.
Art. 5 paragraph 4.
The patient ascertain to have a rare disease, included in Annex 1, by a department of the network, may apply for recognition of the right to exemption to the local health unit of residence, attaching a certificate issued by the same department.
Art. 6, paragraph 1
The patient, that it is exempted, is entitled to health care benefits included in the essential levels of care, effective and appropriate to the treatment and the disease from which he/she suffers, monitoring and for the prevention of further aggravation

DECREE PRESIDENT OF THE COUNCIL OF MINISTERS 12 January 2017
Definition and update of the essential levels of care, referred to in Article 1, paragraph 7, of legislative decree 30 December 1992, n. 502.
Art. 52
People with rare diseases
People affected by rare diseases specified in Annex 7 to this Decree are entitled to exemption from participation in the cost of related health care benefits.

ORPHAN DRUGS

Patients with rare diseases can not be excluded from science and the progress of treatments, as they have the same rights as all the ill. In order to stimulate research and development of orphan drugs, the authorities have adopted incentives in this area. The beginning can be made to coincide with 1983, with the adoption of the Orphan Drug Act in the United States, followed by Japan and Australia in 1993 and 1997; Europe approved in 1999 the creation of a unified policy for orphan drugs for all countries.

The classification of orphan drugs then takes place in Europe at EU level in accordance with Regulation (EC) No 141/2000, and takes into account both the target (rare diseases), as well as the fact that the marketing of a drug intended to treat a rare disease does not always allows for the recovery of the capital invested for its research. Moreover, even a substance to be used for the treatment of a frequent disease could not allow for an adequate return on investment, and thus have an indication as an orphan drug.

Concretely, the rule for the classification of orphan drugs are medicines that:

- treat rare diseases or diseases for which without incentives the investment required to commercialize the drug is unlikely to be profitable
- they are serious conditions (ie involving threat to life or chronically debilitating)
- that there is no satisfactory method of diagnosis, prevention or treatment or the drug brings significant benefits compared to existing ones

The "license" of orphan drug will be forfeited at the request of the sponsor, loss of patent protection or when it is established the loss of even one of these requirements.

NORMATIVE FRAMEWORK

REGULATION (EC) No 141/2000 on orphan medicinal products.

Art.3

A medicinal product shall be designated as orphan medicinal product if its sponsor can demonstrate:

1. That it is intended for the diagnosis, prevention or treatment of a disease that leads to a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU Community when the application is made, or

that it is intended for the diagnosis, prevention or treatment in the EU Community of a disease which involves a threat to life, of disease seriously debilitating or serious and chronic affection, and that it is unlikely that, without incentives, the marketing of the medicinal product in the EU Community would generate sufficient return to justify the necessary investment;

2. that there are no satisfactory methods of diagnosis, prevention or treatment of the condition authorized in the EU Community or, if such methods exist, that the medicinal product will be of significant benefit to those affected by that condition.

Point No. 1 of the Preamble.

Some conditions occur so infrequently that the cost of development and marketing of a medicinal product to diagnose, prevent or treat is recovered by the expected sales; the pharmaceutical industry would not be willing to develop the medicine under normal market conditions; these medicinal products are therefore defined «orphan drugs».

Article 5, paragraph 12

A medicinal product which has been designated as an orphan medicinal product is deleted from the EU Community Register of Orphan Medicinal Products:

a) at the sponsor's request,

b) where it is established before the granting of the marketing authorization that the medicinal product in question no longer meets the criteria set in Article 3

c) at the expiry of the market exclusivity period referred to in Article 8.

NUMBER OF ORFAN DRUGS

Of the 81 recommendations issued by Ema in 2016 for drug approval, 16 are drugs that have been labeled as orphans, 19.7%. Seven of these drugs, 43.75%, are oncologic drugs, the most developed area, followed by the haematological area with 25% of drugs (4 drugs), and metabolic area with 18.75% (3 drugs) And from hepatic and immunological areas with 6.25% (1 approved drug for each).
18.75% Of Authorized Orphan Drugs Were Subjected To An Accelerated Procedure (3 Drugs), Six Are Orphan Drugs That Have Received Marketing Authorization, 37.5%. Of The 16 Orphan Drugs Authorized, Only 2, Both Oncologic, Have Undergone The Accelerated Procedure And The Marketing Authorization.
For One Of The Approved Orphan Drugs, The Marketing Authorization Was Issued In Exceptional Circumstances Related To Metabolic Pathology.
Currently, in the EMA register, drugs with orphan designation are 94. Of these, 86.2% are authorized for one indication (81 drugs), approximately 9.6 is authorized for two different indications (9) drugs for more than three indications (4 drugs).

By 2015, orphan drugs authorized by EMA are 87, of which 66 (including the 13 products classified with the C-nn reimbursement range) are marketed in Italy at 31 December, 2015.
Of the 21 remaining medicines:
11 products are awaiting the allocation of the C-nn range
For two medicinal products, the related refinancing and price negotiation questions have never been submitted by the respective pharmaceutical companies.
8 medicines are accessible on the territory via additional distribution channels (Law 648 and Article 8 of Law 326/2003) that the Italian Medicines Agency provides to patients.

In the year 2015, spending of orphan drugs, including the purchase by public health facilities and the provision of public health care assistance, amounted to about 1.2 billion euro, corresponding to 5.5% of spending for pharmaceuticals.
The impact of spending on orphan drugs classified as non-reimbursable by SSN, is 0.85%, 0.11% in 2014, compared to total orphan drug spending.

In terms of consumption, however, 10.3 million doses of orphan drugs have been consumed in 2015, ie just 0.04% of pharmaceutical consumption

The incidence of consumption of orphan drugs not reimbursed by the SSN on total consumption of orphan drugs is 1.5%, up from the previous year (0.0007%).

In relation to therapeutic categories, 49% of expenditure was used for antineoplastic and immunomodulatory agents followed by 20% for gastrointestinal and metabolic drugs and 11% for cardiovascular system medicines.
In terms of consumption, 41% of orphan drugs are absorbed by antineoplastic and immunomodulatory agents followed by cardiovascular system drugs (13%) and nervous system drugs (11%).

INCENTIVES FOR ORPHAN DRUGS

In order to encourage the pharmaceutical and biotechnology industry to devote itself to the research and development of orphan drugs and to foster the development of knowledge of these diseases, the EU has identified a number of incentives for the sector.
The European Council, with Recommendation 08.06.2009, emphasized the importance of a European level interaction for Member States sharing data on the therapeutic or clinical value of the orphan drug in order to reduce waiting times for access to these medicines by subjects with rare disease. Incentives are then envisaged, both at European and national level, in terms of simplification and acceleration of authorization procedures. These incentives are dealt with in the following paragraphs.

RESEARCH ON ORPHAN DRUGS

Research is the tool to increase knowledge about rare diseases. Research generally conducted on rare diseases does not appear sufficient in relation to the number of pathologies identified and their heterogeneity. For this reason, in order to stimulate research in the field of rare diseases, European and national, various initiatives are identified.

Research on rare disease currently has three major funding levels:

- International: IRDiRC, created in 2011, aims to foster international collaboration in research on rare diseases. In order to reach the ambitious objectives of the Consortium, firstly, it is necessary to strengthen the clinical activity to make homogeneous data and samples available; transferable preclinical and clinical research should be promoted; ethical and regulatory procedures should be streamlined
- European: Since 1990, Europe has identified rare diseases as one of the priority areas of research within the EU Framework Programs for Research and Technological Development (FP)
- National: AIFA finances independent research with a part of the 5% contribution paid by the pharmaceutical companies as provided by the AIFA Act (Law No. 326/2003). Part of this fund is intended to carry out research on the use of medicines and, in particular, clinical comparative trials between medicines to demonstrate added therapeutic value, as well as on orphan drugs and rare diseases. Each year an announcement of selection is made for the SSN structures, research institutes, universities and non-profit organizations on the topics considered priority.

There are other dedicated funds, some are intended for initiatives in the field of medicines, others are provided through the announcements of selection issued by associations and private or non-profit foundations.

In addition to the public sector, the private sector also intervenes in research; Many of the resources used in the experimentation come from private companies.

In this regard, in the National Report on Clinical Trials of Medicines 2015 on 2014 data, the number of clinical trials on medicines for the treatment of rare diseases is 23.5%, with 139 out of 592 ongoing studies in 2014; Of these 44.6% (62 studies) in phase III of the experiment and 38.8% in phase II.

Much of the costs incurred for clinical trials on these drugs are financed by private companies, in fact 74.8%, while the remaining 25.2% is funded by nonprofits. Experimentation subsidized by profit entities constitutes for 86.8%, by international clinical trials; the experiments carried out by nonprofit entities constitutes 80%, by national clinical trials.

NORMATIVE FRAMEWORK
Law 326/2003 ***Article 48, paragraph 19*** *The resources allocated to the fund referred to in paragraph 18 shall be allocated by the Agency:* *a) 50%, for the establishment of a national fund for the use of orphan drugs for rare diseases and medicines which represent a hope for treatment, pending marketing, for particular and serious diseases*

b) for the remaining 50 per cent:
1) the creation within its own structures of an independent drug information center;
2) the realization, in concert with the regions, of an active pharmacovigilance program through structures identified by the regions, with the aim of providing counseling and continuing education for general practitioners and free choice pediatricians in collaboration with organizations of category and relevant scientific societies and universities;
3) research on the use of drugs and, in particular, clinical comparative trials between drugs to demonstrate added therapeutic value as well as on orphan drugs and life-saving medicines, including through announcements of selection to IRCCS, universities and regions;
4) other information activities on drugs, pharmacovigilance, research, training and staff training.

AUTHORIZATION FOR MARKETING

Regulation (EC) No. 726/2004 stipulates that certain types of medicines, including orphan drugs, should be subject to a "centralized" procedure to receive marketing authorization.
This procedure is conducted by EMA, the European Medicines Agency, through its Committee on Human Medicinal Products (CHMP). Following the scientific evaluation of the documentation submitted by the applicant, the Committee issues an opinion which is subsequently transmitted to the European Commission. In turn, the Commission issues a Decision which is binding on all Member States. The centralized procedure requires a time of 210 days.
At national level, the European Assessment Office has a major role for medicines authorized through the centralized procedure, which carries out a scientific evaluation of innovative and high-tech medicinal product dossiers.
For these drugs, the AIFA European Assessment Bureau, with a degree of transposition, classifies the drug in a specific section dedicated to drugs that have not yet been evaluated for reimbursement (Class C (nn)).
Class C (nn) can be considered as a provisional class, in which the drugs that have not yet been evaluated for redeemability are inserted, the same was established by law no. 189/2012.

Regulation (EC) No 141/2000 on Orphan Medicinal Products has introduced the possibility for manufacturers of such medicinal products to request a prior opinion from EMA on the various tests required to demonstrate the quality, safety and effectiveness of the medicine; The Regulation also provides for the establishment of a procedure for the development of orphan drugs, which consists of regulatory advice by the Agency, for the definition of the content of the application for authorization. Furthermore, the European Community and subsequently Member States, according to the rules set out in the Regulation, agree not to grant and accept other AIC for similar medicinal products, with the same therapeutic indications, for a period of ten years, consequently a period of protection.

In order to encourage the production of orphan medicinal products, the European Union has foreseen, for certain categories of medicinal products that meet unsatisfied medical needs, the possibility of granting marketing authorizations based on less complete data than those normally required. To this end, reference is made to:
a. To the marketing authorization
b. To the marketing authorization issued under exceptional circumstances.

THE MARKETING AUTHORIZATION.

The marketing authorization, governed by Regulation (EC) No. 507/2006, involves the rapid approval of a drug on the basis of less complete clinical data than those generally required. This form of authorization may be required for a medicinal product intended for unmet medical need for a severely disabling or life-threatening illness, for a rare disease or for use in emergency situations in response to a threat to public health. In order to achieve the right balance between reducing the time to access to medicines and medicinal products authorization based on an unfavorable risk / benefit ratio, should be subordinate to specific obligations of the marketing authorization. It should, in fact, require that the holder complete or initiate certain studies to confirm

that the risk / benefit balance is positive and resolving any questions concerning the quality, safety and efficacy of the product.
The marketing authorization may be issued when the Committee considers that although no comprehensive clinical data on the safety and efficacy of the medicinal product are provided, the risk / benefit ratio of the medicinal product is respected, when the applicant may subsequently provide complete clinical data, when the medicinal product is intended to meet unsatisfactory medical needs and, finally, where the public health benefits deriving from the immediate availability on the market of the medicinal product in question exceed the risk inherent in the fact that additional data is still needed.
Such authorization shall be valid for one year and may subsequently be renewed. The drug developing company is required to conduct further studies to provide complete data, so that it can be converted to a standard authorization.

MARKETING AUTHORIZATION ISSUED IN EXCEPTIONAL CIRCUMSTANCES

The authorization shall be granted in exceptional circumstances which may be granted provided that the applicant establishes specific mechanisms for the safety of the medicinal product and informs the competent authorities of any inconvenience associated with the use of the medicinal product.
Conditional AIC differ from marketing authorizations issued under exceptional circumstances, which generally refer to very rare diseases. Both procedures are provided for in Article 14 of Regulation (EC) No. 726/2004, respectively, paragraphs 7 and 8. However, while the AIC conditioner is released before all the data is available, and will subsequently be supplemented by the missing data, for a marketing authorization issued under exceptional circumstances, it will never be possible, in principle, to constitute a complete dossier.

At national level, a process is being provided to facilitate quick access to orphan drugs, Law No. 189/2012 provided for the possibility for the pharmaceutical company to ask for price and reimbursement to AIFA shortly after CHMP has issued a positive opinion and, therefore, even before the European Commission has granted Community authorization for the marketing of the drug. This derogation from the normal procedure is related to orphan drugs, medicines that can be used exclusively in hospital and drugs of exceptional therapeutic relevance.
With Law no. 98/2013, AIFA has been assigned the task of prioritizing orphan drugs and of exceptional therapeutic relevance, with a maximum 100-day evaluation time. (So-called "fast track authorization").

NORMATIVE FRAMEWORK

REGULATION (EC) No 141/2000 concerning orphan medicinal products
Art. 8

The Community and the Member States shall not accept any other applications for authorization, grant other marketing authorizations or accept requests for extension of marketing authorizations for existing medicinal products with the same therapeutic indications for a marketing authorization for a period of ten years.

1. Before submitting an application for a marketing authorization, the sponsor of an orphan medicinal product may request an opinion from the Agency on the performance of the various tests and tests required to demonstrate the quality, safety and efficacy of the medicinal product. Medicinal product in accordance with Article 51 (j) of Regulation (EC) 2309/93.

2. The Agency shall establish a procedure for the development of orphan medicinal products, which shall provide regulatory advice for the definition of the content of an application for authorization in accordance with Article 6 of Regulation (EEC) 2309/93.

REGULATION (EC) No 726/2004 sets Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
Article 14, paragraph 8

Upon consultation of the applicant, an authorization may be issued subject to certain specific obligations,

which are reviewed annually by the Agency. The list of such obligations is made available to the public. By way of derogation from paragraph 1, such authorization shall be valid for one year, renewable. The Commission shall adopt a regulation to set the procedures for granting such authorization. This 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).

REGULATION (EC) No 507/2006 authorizing the placing on the market of medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004.

Point n. 2 of the Premises.

However, in the case of certain categories of medicinal products, in order to meet unsatisfied medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorizations based on less complete data than those normally required and subject to obligations, specifically "conditional marketing authorizations".

Point n. 6 of the Premises.

The marketing authorization is issued before all the data is available. However, it is not intended to remain indefinitely conditioned. When missing data is provided it should rather be possible to replace it with a non-conditional marketing authorization, ie not subject to specific obligations.

REGULATION (EC) No 507/2006 Of 29 March 2006

Concerning the marketing authorization for medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council

A marketing authorization may be granted when the Committee considers that despite the lack of complete clinical data on the safety and efficacy of the medicinal product, all of the following conditions are met:

a) the risk / benefit ratio of the medicinal product as defined in Article 1 (28) of Directive 2001/83 / EC is positive;

b) it is likely that the applicant may subsequently provide complete clinical data;

c) the medicinal product meets unsatisfactory medical needs;

d) public health benefits deriving from the immediate availability on the market of the medicinal product outweigh the risk that additional data is still needed.

In the case of emergency situations as referred to in Article 2 (2), a marketing authorization may also be granted in the absence of complete pharmaceutical or preclinical data provided that the conditions set out in points (a) to (d) of this paragraph are respected.

RECOMMENDATION OF THE EUROPEAN COUNCIL 08.06.2009 (2009 / C 151/02)

Which highlighted the need to pool European expertise on rare diseases by sharing Member States' assessment reports on the therapeutic or clinical value of orphan medicinal products at Community level in order to reduce waiting times for access to orphan drugs for people with rare diseases.

LAW No. 189/2012 (so-called BALDUZZI LAW)

Art.5

With the exception of medicinal products for which a claim has been made under paragraph 3, the medicinal products for which a marketing authorization is granted in accordance with Regulation (EC) No 726/2004 of the European Parliament and (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 or Regulation (EC) No 394/2007 of the European Parliament and of the Council of 13 March November 2007, or a Marketing Authorization pursuant to Legislative Decree No 24 of April 24, 2006, are automatically placed in a special section dedicated to drugs not yet evaluated for reimbursement, of the class referred to in Article 8, paragraph 10, letter c) of Law 24 December 1993, no. 537, and subsequent modifications in the case of the submission by the company concerned of any request for different classification under the aforementioned legislative provision. Within sixty days of the date of publication in the Official Journal of the European Union of the European Commission's decision on a Marketing Authorization Application pursuant to Regulation (EC) No 726/2004, Regulation (EC) No 1901 / 2006 or Regulation (EC) No 394/2007, AIFA shall publish in the Official Journal a decision on the classification of the medicinal product in accordance with the first period of this paragraph and its supply

arrangements. For medicinal products authorized under Legislative Decree no. 219, the indications of classification under the first period of this paragraph and of the supply arrangements are included in the marketing authorization. In any case, prior to the commencement of marketing, the marketing authorization holder is required to notify AIFA of the ex-factory price and public price of the medicinal product. The provisions of this paragraph shall also apply to medicinal products subject to parallel importation.

Art.12, paragraph 3

It determined that the pharmaceutical company may apply for price and reimbursement from AIFA immediately after the release of a positive opinion from CHMP and, therefore, even before the European Commission has released a Community authorization to market the drug.

DECREE LAW NO. 69/2013

Article 44, paragraph 4-ter amending Law n.189 / 2012 with the introduction of an art. 5-bis

"The AIFA evaluates for the purpose of classification and reimbursement by the National Health Service the drugs referred to in paragraph 3, for which an application was filed for classification referred to in paragraph 1, accompanied by the necessary documentation, as a priority and giving them priority over pending proceedings at the date of classification application referred to in this paragraph, including through the setting of extraordinary meetings of the relevant commissions. In such a case, the term referred to in paragraph 4, first period, shall be reduced to 100 days. (So-called "fast track authorization").

PRICING OF ORPHAN DRUGS

Drug pricing is a national competence exercised in Italy by AIFA.
Orphan drug regulations follow the same indications of all other medicines, although some of them are of particular relevance in the specific case.
The price at which a medication will eventually be repaid by the SSN is the result of a negotiation between the company requesting its marketing on the national territory and AIFA.
The latter must comply with the following criteria:

- Positive cost / benefit ratio: The medicine is considered useful for the treatment of pathologies for which there is no effective therapy, or provides a more adequate response than medications already available for the same therapeutic indications
- Risk / benefit ratio more favorable than drugs already available for the same indications Assessment of the economic impact on SSN
- Better cost / daily compared with products of the same effectiveness
- Estimate of the available market shares
- Comparison with prices and consumption of other European countries.

In assessing the efficacy and price of a drug, AIFA is supported by the Scientific Technical Committee (CTS) and the Committee on Pricing and Reimbursement (CPR) and the data provided by the National Observatory on Use of Medicines (OSMED).

Note that AIFA therefore adopts a multi-dimensional approach, namely the HTA, which must (among other things):

- Provide for government expenditure on pharmaceuticals in a context of economic and financial compatibility and competitiveness of the pharmaceutical industry while maintaining the economic balance of the fixed ceiling for contracted and hospitalized pharmaceutical spending
- To ensure innovation, efficiency and simplification of registration procedures, in particular to establish rapid access to innovative medicines and medicines for rare diseases
- To encourage and reward R & D investment in Italy by promoting and rewarding innovation
- To interact and interact with the community of the patient associations and with the medical-scientific world and the productive and distributive businesses

As is clear, some rare disease-specific and orphan drug-referrals point to a particular focus on the industry, which, ultimately, has to mediate potential conflicts between efficiency and sustainability criteria.
In other words, there is no derogation from the cost-effectiveness criterion, which guarantees the efficiency of the decisions, but where the price compatible with this criterion is not sufficiently profitable for the Company, ethical evaluations come into play (rare disease rights to 'Access') that are economical (profitability and incentive for research), which are reflected in the requirement for economic impact assessments of SSN, marketable shares, prices and consumption in other countries, objective for an incentive for innovation and research.
In practice, studies have shown that the price of orphan drugs is on average consistent with cost-effectiveness criteria (Picavet et al, 2015), but with a strong variability, explained by rare disease epidemiology. The latter, for example, range from a prevalence in Italy to about 30,000 cases to a few dozen, heavily influencing the chances of turnover and hence return on investment. Consequently, the price is generally adequate, resulting in inversely proportional to the size of its market.
This regularity is also evident in Italy, as shown by Messori et al. (2010) and confirmed by Medic et al. (2017), in particular for ultra-rare pathologies.
Always in order to protect the return on investment, orphan drugs in Italy are exempted from the pay-back mechanism, which includes the leveling of excess expenditures incurred by pharmaceutical companies.

NORMATIVE FRAMEWORK

LAW No. 147/2013 (STABILITY LAW 2014)
Article 1, paragraph 228

In article 15, paragraph 8, of decree-law 6 July 2012, n.95, converted, with modifications, by law 7 August 2012, no. 135, the following changes are made:

a) in point (h), after the words: "concerning medicinal products" the following shall be inserted: "non-orphans and those";

b) in point (i), after the words: 'concerning medicinal products' the following shall be inserted: 'non-orphans and those';

c) after letter (i) the following is inserted:

(I) to (i) shall also apply to medicinal products which comply with the requirements set in Regulation (EC) No. 141/2000 and listed in the European Medicines Agency EMEA / 7381/01 / and of 30 March 2001, as well as other medicines, to be identified by special resolution of AIFA, among those already in possession of the marketing authorizations intended for the treatment of rare diseases and meeting the criteria set in Article 3 of same Regulation 141/2000 and subsequent amendments, even though they were approved before the date of entry into force of that Regulation;

DECREE-LAW 6 JULY 2012, N.95
Article 15, paragraph 8, letter i)

In the case of exceeding budget attributed to the company holding the status of orphan drugs in accordance with Regulation (EC) no. 141/2000 ((of the European Parliament and of the Council of 16 December 1999)), which do not have the characteristics of innovative medicines ((the percentage of excess attributable to such medicines is distributed)) for the purposes of the leveling, gross ofVAT, among all the holders of AIC in proportion to the respective turnover figures for non-innovative medicinal products covered by patent.

Rules for the organization, operation and organization of the staff of the Italian Medicines Agency
art.1

The organization and functioning of the Italian Medicines Agency, ..., are designed to ensure the Agency's maximum efficiency and effectiveness in relation to the relevance of the powers assigned to it, the protection of the right to health, the unity of the pharmaceutical system, access to innovative medicines and orphan drugs for rare diseases, system of economic balance with respect to spending limits, safe and appropriate use of medicines, investment in research and development in the pharmaceutical sector and strengthening of relations with the agencies of other countries and with the European Medicines Agency (EMA).

INSIGHTS

THE MAIN INTERVENTIONS IN RARE DISEASES AND ORPHAN DRUGS

INTERNATIONAL REGULATION

1983 - USA, ORPHAN DRUG ACT

The Orphan Drug Act is a federal law defining the legal status of orphan drugs. This law defines 'orphan drug' in relation to the prevalence (frequency) of the disease. In the United States, the concept of 'orphan drug' does not simply cover pharmaceutical or biological products, but also medical devices and dietary products. Orphan status allows the drug to benefit from the incentives to develop these products up to the marketing authorization. This law will be the model for the subsequent European legislation on orphan drugs.

EUROPEAN REGULATION

1999 - DECISION No 1295/1999 / EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 29 APRIL

It has adopted a 1999-2003 Community Action Program on rare diseases with the objectives of: improving scientific knowledge on rare diseases and creating a European information network for patients and their families; training and updating healthcare professionals to improve early diagnosis; to strengthen international collaboration between voluntary organizations and professional organizations engaged in assistance; support rare disease monitoring in Member States.

2000: THE DEFINITION OF RARE DISEASE

Rare diseases have been identified by the EU as one of the public health sectors for which collaboration between the Member States is crucial and since 1999, with Decision no. 1295, have been the subject of Community recommendations which led to the adoption of a series of programs with broadly shared objectives. According to Regulation no. 141 of 2000 issued by the EC are considered rare diseases with a prevalence of no more than 5 per 10,000 inhabitants (0.05 per cent of the population). Many pathologies, however, are much rarer at just a rate of 0.001%, ie one case per 100,000 people.

These are heterogeneous pathologies, with similar care issues, which need to be dealt with globally and require special and specific protection for diagnostic difficulties, clinical severity, chronic progression, disabling outcomes, and onerous treatment.

2000 - EU, COMMUNITY REGULATION 141

The Regulation established a European Community procedure for the awarding of the status of orphan medicinal products by providing incentives for the research, development and marketing of such orphan medicinal products. Specifically:

- Market exclusivity
- Assistance for protocol processing
- Other incentives: Qualified orphan medicinal products may benefit from incentives made available by the European Community and the Member States in order to promote the research, development and marketing of orphan medicinal products, and in particular the measures of aid for research for small and medium-sized enterprises under the framework programs for research and technological development.

2000 - REGULATION (EC) No.847

The Commission finds, in the regulation in question, the criteria required to obtain the status of an orphan medicinal product. As well as the definition of << similar >> and << clinically superior >>.

2003-2008 - FIRST EUROPEAN COMMUNITY PROGRAM

The first program called for the added value of patient organizations with rare diseases, to create and share knowledge in the various rare diseases environments.

2004 - COMMISSION DECISION 2004/192 / EC
It established the Rare Diseases Task Force (RDTF) at the Directorate General of EC Health and Consumer Protection (EU - DG Health and Consumer). The RDTF, composed of experts from the various Member States, representatives of EMEA and Patient Associations, Research and Public Health Managers on EC-funded rare diseases, had the task of assisting the European Commission (EC) in promoting best strategies for the prevention, diagnosis and treatment of rare diseases, recognizing the added value of coordinating actions on a European scale. Specific objectives included improving information on rare disease diagnosis, screening, treatment and care; The promotion of networks of expert centers for the diagnosis and treatment of rare diseases; Promoting the surveillance and availability of high quality and comparable epidemiological data at European level; The promotion of the development of international rare diseases classification and coding systems, also in collaboration with the World Health Organization (WHO), and the promotion of good clinical practice to improve the quality of life of people with rare diseases.

2004 - REGULATION (EC) No. 726
The regulation in question provides for the establishment of an European Community procedure for the authorization, supervision and pharmacovigilance of medicinal products for human use. In particular, it is foreseen that AIC of orphan medicinal products in the EU must follow the central authorization procedure. Furthermore, the Committee for Medicinal Products for Human Use (CHMP) may issue guidelines on compassionate use programs.

2006 - REGULATION (EC) No. 1901 (PEDIATRIC MEDICINALS)
That regulation extends the market exclusivity period for orphan medicinal products to twelve years if the AIC application includes the results of all the studies carried out in accordance with the approved pediatric investigation plan.

2006 - REGULATION (EC) No. 507
This Regulation establishes a conditional marketing authorization procedure. This procedure also extends to drugs defined as orphans in accordance with Regulation No. 141/2000.

2007 - EU: RARE DISASTERS AS A PRIORITY ACTION SECTOR
The European Commission, in its White Paper "A Common Health Commitment: EU Strategic Approach for 2008-2013" of 23 October 2007, which elaborates the EU Health Strategy, identified rare diseases such as: Priority action area.

2008 - COMMUNICATION FROM THE EUROPEAN COMMISSION TO THE EUROPEAN PARLIAMENT TO THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS "RARE DISEASES: A CHALLENGE FOR EUROPE", 11 NOVEMBER 2008
It outlined the European Community support strategy for Member States in the diagnosis, treatment and care of European citizens affected by rare diseases, developing it in three main areas: enhancing the recognition and visibility of rare diseases; support national plans or strategies for rare diseases in Member States; strengthening co-operation and coordination for rare diseases at European level.

2008-2013 - SECOND PROGRAM OF EUROPEAN COMMUNITY ACTION ON RARE DISEASES
The second program identified one of the main lines of action, the exchange of information through existing networks for rare diseases, and the development of strategies to improve transnational cooperation and coordination of activities at European level.

2009 - EU COUNCIL RECOMMENDATION OF THE EUROPEAN UNION, 8 JUNE 2009
With this recommendation, the EU Council invited Member States to draw up and adopt, in the framework of their health and social systems, national plans and strategies for rare diseases, preferably by 2013, on the basis of the guidelines and recommendations of the European project EUROPLAN; Ensure that rare diseases are

properly encoded and traceable in all health information systems while respecting national procedures, encouraging their proper recognition in national support and repayments systems based on the International Classification of Disease (ICD); To foster rare diseases research and to promote the participation of researchers in RTD funded research projects at various levels, including the EU Community; Locate expert centers in their national territory by the end of 2013 and assess the possibility of promoting their creation; To promote the participation of such centers in European networks; To support the sharing, at European level, of best practice in diagnosis and medical care, training of operators, the development of European guidelines on diagnostic and screening tests; Consult patients on rare diseases policies, facilitate patient access to up-to-date information; To promote the activities of patient organizations, including awareness-raising, training, information exchange and best practice, network building and the involvement of more isolated patients; To ensure, in cooperation with the EU Commission, the use of appropriate funding and cooperation mechanisms, the long-term sustainability of the infrastructures created in the field of information, research and assistance for rare diseases.

2010 - DECISION OF THE EC No. 2009/872 / EC, 30 NOVEMBER, 2009
With this decision, the European Committee of Experts on Rare Diseases (EUCERD) was set up, replacing the RDTF. The Committee's objective is to assist the EC in the elaboration and implementation of EUCommunity action in the field of rare diseases, in cooperation with Member States, the European public research and public health authorities and other actors working in the sector.

2014 - ERN - European Reference Networks. Commission decisions (2014/286 / EU and 2014/287 / EU).
Rare diseases expertise centers are identified by Member States as "expert" structures for the diagnosis and treatment of rare diseaes patients in a defined geographic area. They include or co-ordinate multidisciplinary skills, contribute to developing diagnostic-therapeutic protocols, guidelines and good clinical practice and are linked to specialized laboratories and other facilities (eg rehabilitation), participate in scientific research activities, contribute to the training of doctors, paramedics and non-medical practitioners, provide information and collaborate with patient associations. They are linked to other national and European expertise centers

2014 - REGULATION (EU) No. 536
With this Regulation, the EU recommends the opportunity to encourage the development of orphan drugs and medicines intended for people with serious, debilitating and often potentially lethal diseases such as ultra-rare diseases.
Member States should carry out a rapid but thorough assessment of clinical trials on highly lethal and debilitating clinical conditions for which therapeutic options do not exist or exist to a limited extent.

ITALIAN REGULATIONS

2001 - DM 279/2001, THE LAW LAW OF RARE DISEASES
The Ministerial Decree No. 279 of 2001 provides specific forms of protection for people with rare diseases and has established the national network for the prevention, surveillance, diagnosis and treatment of rare diseases. The network consists of accredited centers, preferably hospitals, specifically designated by the Regions, having documented experience in specific diagnostic or therapeutic activities for rare diseases and interregional centers which, in addition to coordinating the departments of the network, manage the Interregional Registry of rare diseases (in co-ordination with the National Register established at the Institute of Higher Health), exchange of information with other centers and competent international bodies, information to citizens and associations of patients and their families with regard to rare diseases and the availability of medications. The Decree lists the rare diseases for which the right to exemption from participation in the cost of related health care services is recognized. In fact, not all low prevalence pathologies presume exemption from participation at the cost of health care, but only those listed in the DM 279/2001.

2008 - CREATION OF THE NATIONAL RARE DISEASE CENTER (CNMR)
In 2008, with Decree No. 157, the CNMR (National Center for Rare Diseases) was established at the Institute of Higher Health with a mission of research, advice and documentation on rare diseases and orphan drugs aimed at prevention, treatment and surveillance.

2012 - MINISTERIAL DECREE 158
Established the reformulation of rare diseases.

2012 - LAW No. 135 OF 7 AUGUST
The law of August 7, 2012 No. 135 and the subsequent DL No. 158 of 13 September 2012 "Decree Balduzzi". In particular, in the event of exceeding the ceiling of hospital spending at the national level, holders of orphan medicinal products as far as concerned with national excess are excluded from the balancing of the budget.

2013-2016 - THE FIRST NATIONAL RARE DISEASE PLAN
The National Rare Disease Plan 2013-2016, approved at the State-Regions Conference on 16 October, 2014, analyzes the most critical aspects of care, focusing on the organization of the network of centers, the monitoring system, the problems associated with coding of rare diseases and databases, but above all on the diagnostic and care path, not forgetting the tools for therapeutic innovation and the role of the associations. The objective of the plan is the development of an integrated, global and mid-term strategy on rare diseases, centered on the needs of the person and his family and defined by the involvement of all stakeholders.

2016 LAW ON ENLARGED NEONATAL METABOLIC SCREENING
Law No.167 / 2016 "Provisions on Neonatal Diagnostic Observations Mandatory for the Prevention and Treatment of Hereditary Metabolic Diseases" approved on 4 August 2016 and in force since 15 September 2016 provides for the obligation for all regions to offer all new born enlarged neonatal metabolic screening for about 40 rare metabolic diseases for which effective therapies are available or are coming. The law is still in the first phase of implementation.

2017 - DECISION OF THE PRESIDENT OF THE MINISTERIAL COUNCIL OF 12 JANUARY
The new Decree completely replaces the DPCM on 29 November, 2001, which had for the first time defined the activities, services and benefits that the National Health Service (SSN) is required to provide to all citizens for free or for a ticket fee, with the resources collected through general taxation. The Decree also updated the lists of rare, chronic, and disabling diseases that entitle the exemption from the ticket by inserting more than 110 entities, including rare single-group and group diseases, and 6 new chronic diseases.

GLOSSARY

AIC: marketing authorization for a medication.

AIFA (Italian Agency of Medicines): the body that deals with the evaluation of new therapies and the marketing authorization in Italy.

EC: European Community

CHMP: The Committee for Medicinal Products for Human Use, responsible for the preparation of EMA opinions on all matters relating to medicinal products for human use.

CNB: National Committee for Bioethics, with the function of supporting the orientation of regulatory operators.

COMP: The Committee for Orphan Medicinal Products, responsible for the positive opinion on the designation of orphan drug.

CPR: AIFA Price and Reimbursement Committee

CTS: AIFA Scientific and Technical Commission

EMA (European Medicines Agency): the body that deals with the evaluation of new therapies and marketing authorization in Europe.

Erns: European Reference Networks

EUCERD: Committee of Rare Disease Experts of the European Union

FDA (Food & Drug Administration): the body that deals with the evaluation of new therapies and marketing authorization in the United States.

FP: Framework Programs for Research and Technological Development

HTA: Health Technology Assessment. It is a multidisciplinary process that synthesizes information on the clinical, social, economic and ethical aspects of healthcare technology in a systematic, transparent and robust manner.

ICD: International Classification of Diseases

IRDIRC: International Rare Diseases Research Consortium

NORD: National Organization for Rare Disorders

WHO: World Health Organization

ORD: Office of Rare Diseases
Orphan Drug Act: It is a federal law defining the legal status of orphan drugs

Orphanet: a mobile portal for rare diseases

OSMED: National Observatory on the Use of Medicines

PNMR: National Plan Rare Diseases

QALY: Quality-Adjusted Life-Year

RD ERNS: Recommendations On Rare Diseases European Reference Networks

R & D: Research and Development

SSN: National Health System

EU: European Union

WEB PORTALS

Within this section you can find references to sites, updated in 2017, from which additional documents of interest can be downloaded.

National Plan for Rare Diseases:
http://www.salute.gov.it/imgs/c_17_pubblicazioni_2153_allegato.pdf

OSMED Report:
http://www.aifa.gov.it/sites/default/files/rapporto_osmed_2015_aifa-acc.pdf

List of Orphan Drugs AIFA:
http://www.agenziafarmaco.gov.it/sites/default/files/lista_farmaci_orfani_31.03.2017.pdf

List of Orphan Drugs EMA:
http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm

Opinion National Committee for Bioethics, "Orphan Drugs for People with Rare Diseases":
http://presidenza.governo.it/bioetica/pdf/Malattie_rare_25112011.pdf

REGULATION (EC) No 141/2000 concerning orphan medicinal products:
http://eur-lex.europa.eu/legal-content/IT/TXT/PDF/?uri=CELEX:32000R0141&from=IT

REGULATION (EU) No 536/2014 on the clinical trial of medicinal products for human use:
http://eur-lex.europa.eu/legal-content/IT/TXT/PDF/?uri=CELEX:32014R0536&from=IT

REGULATION (EC) No 726/2004 laying down EU Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing the European Medicines Agency:
http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_it.pdf

COMMISSION REGULATION (EC) No 507/2006 authorizing the conditional placing on the market of medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council:
http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_507/reg_2006_507_it.pdf

DECREE OF PRESIDENCY OF THE MINISTERIAL COUNCIL 12 JANUARY 2017, Definition and update of essential levels of assistance:
http://www.gazzettaufficiale.it/eli/id/2017/03/18/17A02015/sg

DECREE 18 MAY 2001, No 279
Regulation on the establishment of the national network of rare diseases and exemption from participation tothe cost of healthcare related benefits:
http://www.regione.lazio.it/binary/rl_sanita/tbl_normativa/DM_MinSan_18052001_279.1155205772.pdf

LAW No. 189/2012 (so called BALDUZZI LAW):
http://www.iss.it/binary/ogap/cont/legge_189_2012.pdf

LEGISLATIVE DECREE No. 124/1998,

Redefining the system of participation in the cost of healthcare and exemption regime:
http://www.gazzettaufficiale.it/eli/id/1998/04/30/098G0180/sg;jsessionid=VyN90bmeEB0lItuaW+rrNg__.ntc-as2-guri2a

LEGISLATIVE DECREE No 502 / 1992- Annex 7 (List of exempt rare diseases):
http://www.trovanorme.salute.gov.it/norme/renderPdf.spring?seriegu=SG&datagu=18/03/2017&redaz=17A02015&artp=12&art=1&subart=1&subart1=10&vers=1&prog=001

DECREE LAW No. 69/2013:
http://www.gazzettaufficiale.it/eli/id/2013/06/21/13G00116/sg

LAW NO: 147/2013 (STABILITY LAW 2014):
http://www.gazzettaufficiale.it/eli/id/2013/12/27/13G00191/sg

DECREE LAW No. 95/2012:
http://www.gazzettaufficiale.it/eli/id/2012/07/06/012G0117/sg

PRESIDENCY OF THE MINISTERIAL COUNCIL
Permanent conference on relations between the state, regions and autonomous provinces of Trento and Bolzano, Directory No. 140 / CRS of October 16, 2014:
http://www.statoregioni.it/Documenti/DOC_045256_140%20%20CSR%20PUNTO%201%20%20ODG.pdf

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.

C.R.E.A. Sanità – Consorzio Ricerca Economica Applicata in Sanità
www.creasanita.it
Contacts: barbara.polistena@uniroma2.it

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.
O. MA. R.
www.ossevatoriomalattierare.it
contact: direttore@ossevatoriomalattierare.it

WWW.OSSERVATORIOFARMACIORFANI.IT