

Rare diseases and orphan drugs

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Summary. According to the Regulation (EC) N. 141/2000 of the European Parliament and of the Council, rare diseases are life-threatening or chronically debilitating conditions, affecting no more than 5 in 10 000 persons in the European Community. It is estimated that between 6000 to 8000 distinct rare diseases affect up to 6% of the total EU population. Therefore, these conditions can be considered rare if taken individually but they affect a significant proportion of the European population when considered as a single group. Several initiatives have been undertaken at international, European and national level to tackle public health as well as research issues related to the prevention, diagnosis, treatment and surveillance of these diseases. The development of innovative and effective medical products for their diagnosis and treatment is frequently hampered by several factors, including the limited knowledge of their natural history, the difficulties in setting up clinical studies due to the limited numbers of patients affected by a specific disease, the weak interest of sponsors due to the restricted market opportunities. Therefore, incentives and other facilitations have been adopted in many parts of the world, including in the EU, in order to facilitate the development and commercialization of diagnostic tools and treatments devoted to rare diseases. This paper illustrates mainly the European initiatives and will discuss the problematic and controversial aspects surrounding orphan drugs. Finally, activities and measures adopted in Italy are presented.

Key words: rare diseases, orphan drugs, incentives, small population.

Riassunto (*Malattie rare e farmaci orfani*). Secondo il Regolamento (EC) n. 141/2000 del Consiglio e del Parlamento Europeo, le malattie rare sono condizioni che minacciano la sopravvivenza o creano disabilità croniche che colpiscono non più di 5 persone su 10 000 nella Comunità Europea. Si stima che le malattie rare siano tra le 6000 e le 8000, e colpiscano fino al 6% della popolazione dell'Unione Europea. Queste patologie, quindi, possono essere considerate rare individualmente, ma coinvolgono una porzione significativa della popolazione europea quando vengono considerate nella loro totalità. Sono state intraprese diverse iniziative a livello internazionale, europeo e nazionale per affrontare i problemi della ricerca e di sanità pubblica legati alla prevenzione, diagnosi, trattamento e vigilanza di tali patologie. Lo sviluppo di prodotti farmaceutici innovativi ed efficaci per la diagnosi ed il trattamento delle malattie rare trova spesso diversi ostacoli, quali le limitate conoscenze sulla storia naturale delle diverse patologie, le difficoltà nell'effettuare sperimentazioni cliniche a causa del limitato numero di pazienti affetti da una specifica malattia ed il limitato interesse degli sponsor per le scarse opportunità di mercato. Per questa ragione in molte parti del mondo, anche nell'UE, sono previsti incentivi ed altre facilitazioni per agevolare lo sviluppo e la commercializzazione di mezzi diagnostici e curativi per le malattie rare. Questo articolo illustra principalmente le iniziative intraprese a livello europeo ed analizza gli aspetti problematici e controversi legati ai farmaci orfani. Infine, sono illustrate le attività ed i provvedimenti adottati in Italia.

Parole chiave: malattie rare, farmaci orfani, incentivi, popolazione.

RARE DISEASES

Rare diseases (RDs) are a serious public health problem and represent unique challenges in many Countries. There is no internationally accepted definition for RDs. They are defined by the European Union (EU) as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10 000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic

potential. This definition appeared first in EU legislation in Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products [1].

In the USA the Orphan Drug Act of 1983 defines a RD as "any disease or condition that affects less than 200 000 people in the United States". In Japan, the Japanese Medicines Act of 1993 defines a rare disease as a condition affecting no more than 50 000 people in the country.

RDs are many and diverse diseases characterized by the low frequency in the general population, the

majority of them have genetic origins but a significant number are acquired with the contribution of environmental factors. Onset occurs in about half of them at birth or during infancy, while the rest appear during adulthood. RDs are associated often with premature mortality and long lasting and severe disability. RDs have specific clinical and pathogenetic characteristics, but their social and health impact share a number of common features, which make RDs as a whole to represent a public health issue. Common problems to most RDs include difficult and often delayed diagnosis, frequently caused mainly by the health operators' lack of familiarity with them; limited or lack of information available to the public, medical students and practitioners; scarcity of research projects due to limited resources devoted to the single RD; difficulties in setting up clinical studies due to the scarcity of patients; weak interest in developing medicinal products targeting these conditions due to the unfavourable marketing conditions; limited access for patients to treatments.

Notwithstanding their low prevalence, RDs make up a considerable burden to public health systems due to their numerosity. The European Commission [2] reports that the number of existing RDs is estimated to be between 5000 and 8000, affecting a total of 6-8% of the population – in other words, between 27 and 36 million people in the EU. According to available data the examples of the less infrequent RD include Charcot-Marie-Tooth disease, Retinitis Pigmentosa, Hemophilias, Cystic fibrosis and Duchenne Muscular Dystrophy. Accurate data on the epidemiology of rare diseases are urgently needed at national and international level, in order to support health management policies and studies aimed at development and assessment of treatments.

RDs are not limited by geographical or historical boundaries and global partnerships are rapidly expanding across the community of RDs. Accordingly, as a transnational community of different countries working to develop a common framework, the EU envisages and encourages initiatives at European and Member States level to draw national plans and strategies to tackle the complexity of RDs.

THE EUROPEAN COMMISSION INITIATIVES

The European Commission has acknowledged that a number of healthcare and knowledge issues are common to all rare diseases in spite of the wide variety of their clinical manifestations and has recently promoted the definition of national plans and comprehensive strategies to improve the provision of care to rare disease patients.

The European Commission in its Communication of the 11th of November 2008 to the European Parliament and Council on "Rare diseases: Europe's challenges" analysed comprehensively the issues associated with the provision of care to RD patients

[3]. Following this Communication, the Council of the Health Ministers of the EU acknowledged the need to act in the area of RDs [2] and issued a number of recommendations for actions to be considered by the Member States. They include:

- the integration of relevant national actions in the field of RDs into comprehensive plans or strategies, to be issued by 2013, in order to improve the coordination and coherence of national, regional and local initiatives addressing RD and cooperation between clinical and research centres;
- the development of an appropriate classification and coding, in order to improve the visibility of RDs and their recognition in the national health systems;
- the adoption of a common classification in all EU Member States, the identification of qualified Centres of expertise for diagnosis and care of RD and their participation in European Reference Networks in order to facilitate cooperation among Member States, share knowledge and improve the access of RD patients to high quality care;
- the establishment of an inventory for projects and resources dedicated to RD research, identify needs and priorities and devise financing schemes to support research and facilitate its coordination at national, Community and international levels;
- gathering expertise at Community level in order to facilitate sharing of best practices for diagnosis and care, adequate education and training for health professionals, guidelines on diagnostic tests and population screening, as well as sharing national assessment reports on orphan drug added value.

The Council Document also recommended the involvement of patient representatives in the development of policies and in other activities aiming at patient empowerment, such as awareness-raising, capacity-building and training, exchange of information and best practices and support of isolated patients.

The EU Recommendations reflect some achievements of the ongoing action and commitment of the European Commission. Indeed, to raise the attention and improve the information on RD, the European Commission has, since 1997, given priority to projects that can support the development of a common EU framework: actions envisaged include collecting information on centres of expertise, setting European registries and networks of experts on RD and developing consensus guidelines for newborn screening. The European Commission is also co-funding the project EUROPLAN (www.europlanproject.eu) coordinated by the Italian National Center for Rare Diseases (Centro Nazionale Malattie Rare, CNMR), that aims to promote the implementation of the EU Council Recommendations on RD in the EU Member States (see paragraph on CNMR activities).

Among the 27 EU Member States, national plans or strategies of different complexity and with different aims have been adopted only in few countries,

such as France (the first country to have a RD plan in 2005), Bulgaria, Czech Republic, Greece, Portugal, Romania and Spain [4]. Other EU Member States are currently preparing their plans or strategies. An inventory of the initiatives undertaken in the EU Member States has been jointly produced by the EU Committee of Experts on Rare Diseases (EUCERD) and EUROPLAN [5].

In Italy, a number of initiatives and actions have been undertaken at national and regional level in order to provide quality care to RD patients and to support research as well. Some of these initiatives have anticipated the recommendations at the European Union level.

THE COMPLEX WORLD OF ORPHAN DRUGS

An orphan drug can be defined as a product for the diagnosis, prevention or treatment of a disease that is not economically viable under ordinary marketing conditions.

Several problems hamper the development and commercialisation of these products [6-9]:

- *difficulties in setting up clinical studies*: scarcity of patients and low interest from pharmaceutical companies are among the major obstacles to be overcome in order to actualise clinical studies necessary to develop new medicinal products;
- *challenges in assessing clinical relevance and cost-effectiveness*: the evaluation of orphan drugs is often still in an experimental phase, hampering the possibility of an objective assessment to establish their relevance in clinical practice. However, when the number of patients is extremely limited, a careful balance of patients' right to medical care, cost-effectiveness and safety must be carried out. In particular circumstances, the commercialisation of products with an incomplete assessment with regard to cost-effectiveness has occurred. In such cases a regime of post marketing surveillance is highly recommended in order to gather the missing data for a satisfactory assessment of the cost-effectiveness, the relevance in clinical practice and to improve the safety profile;
- *high costs*: treatment with an orphan medicinal product can be very expensive, thus affordability is a major issue for public health systems and raises concerns among different stakeholders. The problems above mentioned are not exclusively confined to rare diseases but they exemplify and reflect the global debate of the difficulties in bringing new diagnostic and therapeutic tools where they are most required from a public health perspective;
- *insufficient market opportunities*: orphan drugs could be considered an example of the limits of ordinary market conditions. These medicinal products meant for treatment of life-threatening or chronic debilitating conditions affecting only a small fraction of the population have such a

limited market perspectives for recovery of development costs, including the extensive animal and clinical testing required for approval, that they may never become available unless developed at least partially at public expenses, even if some of them could be developed for prestige purposes or as a public service known as "merit good" by pharmaceutical industries.

In order to overcome the critical areas above mentioned, it has been necessary to set up a specific legislative framework to support the development of orphan drugs and make them economically viable.

Historically, the first legislative act was the US Orphan Drug Act in 1983 [10]. A market exclusivity of 7 years, tax credit for clinical trials costs and fee waiver for regulatory activities are among the financial incentives offered to pharmaceutical companies to set up programmes for research and development of new drugs for rare diseases. In addition to the financial incentives, companies are offered protocol assistance, access to specific grants and advice on development. In Japan, the Japanese Medicines Act in 1993 granted a market exclusivity of 10 years and tax credits on any kind of studies. Part 3B of the Therapeutic Goods Regulations 1990 was adopted in Australia in 1997 and offers as an incentive a fee waiver for regulatory activities. In the European Union Regulation (EC) No 141/2000 was adopted in 1999 and implemented in the year 2000. It set up criteria for designation and incentives to promote research, development and marketing authorisation of orphan drugs [11].

The orphan drug designation is based on three elements:

- prevalence or economic criteria;
- seriousness of the condition to be treated;
- existence of satisfactory alternative medicines.

In the following paragraphs the EU regulatory framework will be discussed in greater details.

EU REGULATIONS AND PROCEDURES: EMA AND THE COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

The regulation on orphan medicinal products (OMP) for rare diseases states that the European Medicines Agency (EMA), through its Committee for Orphan Medicinal Products (COMP), is responsible for assessing designation applications from sponsors intending to develop medicines for rare diseases, so-called "orphans".

The COMP (from the website www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000123.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e32) is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

COMP members are nominated by the Member States, and are chosen on the strength of their qualifications and expertise with regard to the evaluation of medicinal products. They serve on the committee for a renewable period of three years.

The COMP is composed of:

- a chairman, elected by serving COMP members;
- one member nominated by each of the 27 EU Member States;
- three members nominated by the European Commission to represent patients' organisations;
- three members nominated by the European Commission on the EMA's recommendation;
- one member nominated by each of the EEA-EFTA states (Iceland, Liechtenstein and Norway);
- one European Commission representative;
- general observers.

Criteria to be met for orphan designation by the COMP are:

- the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five in 10 000 persons in the EU at the time of submission of the designation application (prevalence criterion), or;
- the medicinal product it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development, and;
- either no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such method exists, the medicinal product will be of significant benefit to those affected by the condition.

Companies with an orphan designation for a medicinal product benefit from incentives such as: protocol assistance (scientific advice for orphan medicines during the product-development phase); direct access to centralised marketing authorisation and 10-year marketing exclusivity; financial incentives (fee reductions or exemptions); national incentives detailed in an inventory made available by the European Commission.

Since 1 February 2009, orphan medicinal products are eligible for the following level of fee reductions:

- full (100%) reduction for protocol assistance and follow-up;
- full (100%) reduction for pre-authorisation inspections 50% reduction for new applications for marketing authorisation to applicants other than small and medium-sized enterprises;
- full (100%) reduction for new applications for marketing authorisation only to small and medium-sized enterprises;
- full (100%) reduction for post authorisation activities including annual fees only to small and medium sized enterprises in the first year after granting a marketing authorisation.

In general the dossiers for the COMP approved show several limitations [12]:

- 1) lack of dose finding studies;
- 2) lack of controlled studies. Of active comparator where available, of multicentre Phase III trials with a suitable number of patients (particularly for diseases with a frequency from 5/100 000 to 5/10 000);
- 3) insufficient exposure to the treatment;
- 4) use of surrogate endpoints or weak proof of clinical benefit.

The requirement for follow-up studies for the 10 drugs approved "under exceptional circumstances" will not necessarily be met and in any case many years are likely to pass before the results are known.

This may reflect a general approach to the development of OMPs that might have hampered the approval of other products and could have made the proportion of licensed OMPs out of those applied for lower than that of drugs for common clinical indications.

It is certainly difficult to find a balance between the urgent need for drugs for patients with RDs while guaranteeing at least their quality, efficacy and safety and, when necessary, making comparisons with existing drugs. Probably the lack of reliable methods for evaluating the effect of drugs on small numbers of patients is partly responsible for the general poor quality of the dossiers. Unquestionably, less stringent criteria are acceptable for orphan drugs, than for drugs for more common diseases, particularly in view of the small or very small numbers of patients. However, even when few patients are available at least a Phase II study should be performed, comparing the new treatment with the best available care, to establish the clinical benefit of the new therapy. It must be borne in mind that in a small population it is difficult to assess the safety of orphan drugs, as adverse drug reactions are often much rarer than events adopted as measures of outcome [12].

LEVELS OF EVIDENCE: THE COMMITTEE FOR HUMAN MEDICINAL PRODUCTS AND MARKETING AUTHORISATION

It is very important to highlight the fact that an orphan designation by the COMP does not constitute a marketing authorisation. The assessment of applications for marketing authorizations is performed by the Committee for Human Medicinal Products (CHMP).

As stated in the EU Orphan Regulation, patients affected by rare diseases "deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process" [1]. Marketing authorisation in small populations will be judged against the same standards as for other products, although limitations on patient recruitment will be taken into account. Two regulatory guidelines address the aspects on rare diseases: *The*

guidelines on clinical trials in small population (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf) and the *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design* (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf).

In particular, hierarchies of evidence have been described in the *The guidelines on clinical trials in small population* which usually place in order:

- meta-analyses of good quality randomised controlled clinical trials that all show consistent results;
- individual randomised controlled trials;
- meta-analyses of observational studies;
- individual observational studies;
- published case-reports;
- anecdotal case-reports;
- opinion of experts in the field.

All such forms of evidence provide some information (even anecdotal case reports) and none should be ignored. However, high levels of evidence in drug development come from well-planned and well executed controlled clinical trials, particularly trials that have minimized bias through appropriate blinding and randomization. At their conclusion, the treatment effect should ideally be clinically relevant, confidence intervals for that effect should be narrow, and the effect size statistically significant. Well-planned and well-conducted meta-analyses of such trials will provide even stronger evidence. It must be recognized, that poor meta-analyses will not give reliable conclusions.

In very rare diseases, the combined evaluation of single case studies may be the only way to provide evidence. In such situations, treatment conditions and data collection should be standardized and data should be of high quality and adhere to good clinical practices (GCP) standards. Such studies should be prospectively planned and described in study protocols. A systematic review of all data (including data from other sources) will add weight to the evidence. Also combined analysis of individual case reports or observational studies should be considered.

Generally, for a given size of treatment effect, a larger sample size and/or a smaller variance will result in narrower confidence intervals and more extreme levels of statistical significance.

In summary, there are no special methods for designing, carrying out or analyzing clinical trials in small populations. There are, however approaches to increase the efficiency of clinical trials. The need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results, the latter being the most important.

Guidelines (ICH, CHMP and others) relating to common diseases are also applicable to rare diseases, taking into account the specificity of rarity and therefore the small number of patients.

In situations where obtaining controlled evidence on the efficacy and safety of a new treatment is not possible, the regulatory assessment may accept different approaches if they ensure that the patients' interests are protected.

Detailed knowledge of the pharmacology of a compound may help when designing studies. Pharmacology studies may help identify sources of heterogeneity in patients. Non-clinical pharmacology may sometimes be helpful, especially in conditions where very few patients are available.

Surrogate endpoints may be acceptable but need to be fully justified. Their relation to clinical efficacy must be clear so that the balance of risks and benefits can be evaluated.

Controls and comparator groups are very important. Their absence compromises the reliability of studies.

Patients registers may supply important information on the natural course of disease and may help in the assessment of effectiveness and safety, but of course they should contain high quality data.

It is strongly recommended that scientific advice/protocol assistance be sought during all phases of development to guide sponsors as to the acceptability of their planned approaches for later marketing.

Once the assessment by the CHMP is completed, the outcome is communicated to the European Commission for the final ruling about the centralise authorisation for the commercialisation of the medical product.

EXPENSIVE MEDICINAL PRODUCTS: ORPHAN INCENTIVES

The European Commission's Enterprise and Industry DG published an independent survey on the price of orphan drugs. The survey was conducted by Alcimed and was focused on the price of orphan drugs authorized in the EU and how these prices had been calculated. In addition, the study debates how "sufficient profitability" might be assessed and judged. This latter aspect relates to the operation of article 8 (market exclusivity) of the Orphan Regulation.

Main EU incentives: given the low level of interest of the sponsors, under ordinary market conditions, in developing and marketing medicines intended for small numbers of patients, the European Union offers a range of incentives to support the development of orphan drugs.

To benefit from the incentives, sponsors intending to develop orphan medicines must first submit an application to the EMA requesting "orphan designation" for their product. Once a medical product has been granted orphan status (by the European Commission, following a positive opinion on orphan designation from the EMA's Committee for Orphan Medicinal Products), its sponsor is then eligible to benefit from the following incentives:

- ten years exclusivity from the date of marketing authorization;

- fees reduction: orphan medicinal products designated in accordance with Regulation (EC) No 141/2000 of 22 January 2000, are eligible for reductions of all fees payable under Community rules pursuant to Regulation (EEC) 2309/93, as amended. This includes fees for pre-authorization activities such as protocol assistance (scientific advice), and for products using the centralized procedure: the application for marketing authorization, inspections and post-authorization activities such as variations, annual fees, etc.;
- protocol assistance, a scientific advice, for sponsors intending to develop an orphan-designated medicinal product for marketing authorization. This assistance is particularly useful to companies developing a medicinal product: when there are no or only insufficient relevant details in EU guidelines, guidance documents or draft documents circulated for consultation, or Pharmacopoeia monographs or draft monographs released for consultation; where the company chooses to deviate in its development plan from the available guidance;
- direct access to centralized procedure;
- priority access to EU research programs.

National incentives: they are detailed in an inventory made available by the European Commission (http://ec.europa.eu/index_en.htm).

CONTROVERSIAL POINTS: IS THE COST OF ORPHAN DRUGS FAIR?

The process required to bring an orphan drug to the market can be lengthy and expensive [13]. Whilst basic research is mainly carried out by academic institutions, the translational research is mainly carried out by pharmaceutical companies. In addition the difficulties and costs of clinical trials should be taken into consideration. Finally, approximately 30% of all drugs still fail Phase III trials. From the perspectives of pharmaceutical companies if one also considers the narrow market of orphan drugs, often the result is the high costs of these products to make them economically viable [14].

However, recent episodes have cast strong doubts on this argument.

In recent scientific articles, it has been argued that the increase of the cost of 3,4 diaminopyridine (3,4 DAP) used to treat Lambert-Eaton myastenic syndrome and the congenital myastenic syndrome is not justified and that this is an unintended effect of the EU legislation on orphan drugs. This medication, which has an excellent safety record, had been available to patients for many years and was produced by a small company on an unlicensed basis with a cost of about £ 800 per patient/year. Since another company got the orphan drug designation and has been issued a licence to supply a slightly modified molecule marketed as Firdapse, the cost has increased between a 50 to a 70-fold: from £ 40 000 to £ 70 000 per patient/year. The company used data from the unlicensed version to demonstrate that its drug is safe and effective [15].

In the opinion of the authors [14], the exorbitant price paid by the British NHS is totally unjustified.

Similar episodes have involved other drugs such as N-carbamylglutamate, Sodium phenylbutyrate, Ibuprofen and Indometacin for patent ductus arteriosus, caffeine citrate for apnoea in preterm infants and nitric oxide for pulmonary hypertension [15, 16].

It has been recently suggested [17] that orphan drug pricing contravene competition law, particularly article 102 of the Treaty of the Functioning of the European Union where it prohibits “abuse by one or more undertakings of a dominant position within the internal market or in substantial part of it...Such abuse may, in particular, consist in: (a) directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions...” [17].

The orphan drug market is challenging: on one side there are the costs of developing innovative drugs for rare diseases with little economic profitability due to the limited market opportunities. On the other side, it is imperative to set up prices that are fair and affordable in order to avoid an unnecessary overstretching of the resources of the national health systems. It may be quite difficult to find a fair balance of these competing aspects. However, failure to regulate the orphan drug market in a fair and appropriate manner may result in an impairment of the process of development and commercialisation of innovative orphan drugs, in a deprivation of much needed resources and incentives for innovative and effective pharmaceutical products or in a lack of affordability for many patients due to unreasonable high costs.

In light of the recent experiences European and national regulatory agencies should look at whatever loopholes might be in the present legislation and regulatory framework.

ITALY: INITIATIVES TO TACKLE RARE DISEASES AT NATIONAL AND REGIONAL LEVEL

Italy has adopted a number of measures for the care of patients with rare diseases [4]. The three year National Health Plans, which are intended as directions for actions to be followed by the whole country, have been indicating since 1998 that rare diseases are among the priorities for the health care system. Moreover, in 2001, the Ministry of Health issued a Decree (DM 279/2001) [18] establishing the national network for rare diseases and cost exemptions for related health service provisions. The main aim of this Decree was to set rules for cost exemptions for services included in the essential care levels (LEA: *livelli essenziali di assistenza*) and to identify specific protective measures for rare disease patients. To reach this goal, the Decree established a national network of Centres for the prevention, surveillance, diagnosis and care of rare diseases, the National Register for Rare Diseases. With reference to surveillance, it has included the provision for the

establishment of a national registry of rare diseases, connected to multiregional registries and, through them, the ability to receive epidemiological, clinical and other data from qualified Centres designated by the Regional authorities. The Decree also set a list of rare diseases, including 284 single and 47 groups of rare diseases, to facilitate referral of suspected patients to the appropriate diagnostic Centre, to waive costs for diagnostic tests and to speed up assistance of patients with confirmed diagnoses. The list of rare diseases can be updated based on the progression of scientific and technological knowledge, the epidemiology of diseases and diagnostic and therapeutic pathways. To date an additional 109 conditions have been identified and are waiting for official recognition by the health authorities. Another important provision set out by the Italian Council of Ministers (DPCM of 9 July 1999) [19] was the mandatory performance of the newborn screening tests for three rare conditions: phenylketonuria, congenital hypothyroidism and cystic fibrosis. Indeed, the early identification of patients affected by these diseases before the clinical onset of symptoms, could allow for treatments that prevent the evolution of these diseases into severe disabilities. The Italian health care system has delegated the responsibility for the provision of health services to the regional health authorities. Based on a decision from the State-Regions Conference, a standing inter-regional technical group, made of Regional Representatives, the Ministry of Health and the National Institute of Health, was established in 2002. Their mandate is to ensure the coordination and monitoring of health care activities regarding RDs, with the aim of optimising the operation of the regional networks and safeguarding the principle of equity in healthcare for all citizens. Each Region identified its own reference Centres for rare diseases to be part of the National Network for Rare Diseases. The Regional Centres were identified among those possessing documented experience in diagnostic or specific therapeutic activities and endowed with adequate structures and complementary services (emergency services and services for biochemical and genetic molecular diagnosis). Moreover, by virtue of their competences, four Regions (Marche, Piemonte, Toscana and Valle d'Aosta) adopted a list of rare diseases that was more extensive than the one established at the national level, and two Regions (Toscana and Veneto) have recently decided to undertake population wide newborn screening that has been expanded to cover more than 20 rare diseases. Regional activities that address rare diseases have received 30 Million Euro in financial support based on the Financial Budget of 2007.

As previously discussed, in general pharmaceutical industry has limited interest in the development of drugs intended for the treatment of RD patients, due to the limited market and profit expected. EMA has developed an evaluation process, shared by all EU Member States, for the designation and authori-

zation of medicinal products as orphan drugs, thus ensuring their availability by means of incentives for their production.

In Italy about 43 orphan drugs authorized at a centralized level by the EMA are paid by the Italian National Health Service (NHS) and are available to patients suffering with RDs and some of them are under post-marketing surveillance (see below paragraph "CNMR-Orphan drugs").

However, there is still the possibility, depending on the requests for registration and on the national registration procedures, that some orphan drugs are at least temporarily available in a Country and not in another. Moreover, some drugs used for other diseases, may be presumed to be effective for a rare disease, which is not indicated in the label. A number of general provisions have been issued in Italy, which are of particular advantage for RD patients.

The law 648/96 [20] allows, on the costs of the National Health Service, the use of drugs marketed abroad; the use of drugs not authorized but subject to clinical trial; and the off-label use of drugs.

Law 648/96 ensures that patients with rare diseases can get early access to treatments for conditions with no therapeutic alternatives. According to this law, health operators, patients associations or fellow citizens can request early access to medications available in the European market by submitting a written request to the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) listing the evidence of efficacy available in the scientific literature. The request is eventually discussed by the Technical and Scientific Committee (CTS) of AIFA and approved for clinical use if deemed appropriate. Thus, the medication becomes available to patients with inclusion and exclusion criteria set by AIFA. In addition, the medication is subjected to a program of surveillance. Therefore, such uses need to be authorized by a Scientific Committee and should be reported in a list which is periodically updated. The off-label use of a drug, on the costs of the National Health Service, can be also decided by a doctor, as envisaged by art. 3, paragraph 2 of DL 23/1998 [21], provided that it will be decided patient-by-patient, will not be continuous, is supported by documented evidence and/or results published on internationally renowned journals and no alternative treatments are possible. Finally, a drug, which is not authorized but is subject to Phase II or III clinical trials for the same therapeutic indication, and which appears to result with a likely favourable evaluation of efficacy and safety, can be prescribed to one patients or groups of patients on the costs of the producer [22].

Law 94/98 [23], known as "Legge Di Bella", allows doctors to use, under particular circumstances, drugs in a compassionate way. This enhances accessibility to treatments for patients with rare diseases for which there is no established therapy.

Finally, it is worth to mention the program to promote independent research on orphan drugs that is set up and managed by the Ministry of Health, the

National Institute for Health and the Italian Drug Agency. This program allows clinicians and researchers to develop or assess therapeutic options even in those areas where there is no commercial interest.

Moreover, patients suffering from disabilities associated with RDs are eligible for assistance, including not only compensation for reduced working ability, but also integration at work, on the basis of the current general regulations for civil inability. In particular, Law 118/71 [24] refers to congenital and acquired inabilities, including those of a progressive nature, which result in a permanent reduction in the working ability as well as, for those patients younger than 18, it also covers permanent difficulties related to performing tasks and activities typical of their age. Following this, a legislative decree [25] extended the definitions set by Law 118/71 to include the permanent functional impairments resulting from physical and/or psychical and sensory illnesses. Moreover the definition of inability that applied to patients younger than 18, was extended to cover those older than 65.

THE NATIONAL CENTRE FOR RARE DISEASES

Since 2000, the “Rare Diseases” Unit at the National Institute of Health (Istituto Superiore di Sanità, ISS) has been actively developing a wide array of national and international initiatives on rare diseases, some of which have contributed to the implementation of the Italian Network of Rare Diseases [26]. As a result of the strategic approach, developed over more than ten years, to tackle the public health challenges associated with Rare Diseases, this Unit has been the initial nucleus of the Italian National Centre for Rare Diseases (CNMR, www.iss.it/cnmr), which was formally established at the ISS in 2008, with the mission of research, surveillance and information on rare diseases and orphan drugs, aiming to prevent, diagnose, treat and control these disorders [4, 26]. The Centre hosts a wide range of scientific and technical expertise (genetics, molecular biology, epidemiology, neurology, public health, psychology, sociology etc.) and participates in networks of national and international collaborative activities, which allow for the development of a multidisciplinary integrated approach to rare disease issues. CNMR regularly provides expert advice to the Italian National Health Service, to the Ministry of Health, to the Higher Health Council, to the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and collaborates with the Regions, which are responsible for the provision of health services in the Italian devolved health system. Expert advice on rare diseases is also provided at EU and international level with its ad hoc participation in scientific committee meetings of the European Food Safety Authority; in the formerly named European Commission Task Force on Rare Diseases (DG SANCO), now EUCERD (European Union Committee of Experts on Rare Diseases) and

the Research Advisory Committee (DG Research), as well as in WHO and OECD Committees.

CNMR is currently undertaking several activities:

- *research on rare diseases.* CNMR plays an important role in the coordination and promotion of national scientific and public health research, and participates in the Advisory Committee for European Research. In the framework of an agreement with US NIH, CNMR cares the implementation of a national program of scientific research projects on rare diseases. CNMR scientists carry out research projects on the pathogenesis of selected rare diseases using advanced technologies (e.g.: bioinformatic methodologies, micro-RNA platform and CGH array, fluorescence videomicroscopy and electrophysiology) [27-30]. Moreover, CNMR carries out public health research on matters of relevance to its mission (e.g., epidemiology, service accessibility, identification of patients' needs; patients' quality of life [31-33]; coordinates the EU EUROPLAN project, aiming at facilitating the implementation of the EU Recommendation on rare diseases (www.europlanproject.eu); is partner of E-RARE, an ERA-net project for the improvement of rare diseases research infrastructures (www.e-rare.eu) and of the EU Tender on EU Newborn Screening Practices (www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64);
- *quality of rare diseases diagnostic tests and patient management.* CNMR is part of the OECD Panel of experts for the preparation of Guidelines for quality assurance in molecular genetics tests (34) and in the EU-funded project “Multi-National External Quality Assay (EQA) programs in Clinical Molecular Diagnostics” [35]. CNMR is member of the European Molecular Genetics Quality Network and participates in the EU-funded EuroGentest excellence network, aiming at the standardisation and harmonisation of quality of genetic testing in EU Member States. CNMR coordinates the National External Quality Assessment schemes, for a number of molecular genetic and cytogenetic rare diseases diagnostic tests carried out in Italian public laboratories [36-41]. CNMR is implementing a program of guidelines for the management of rare disease patients; up to now several guidelines have been elaborated for the integrated multidisciplinary approach to the management of several rare diseases and syndromes. Moreover, CNMR monitors the publication, collects and makes available in its website guidelines prepared by other national and international organizations;
- *primary prevention.* CNMR coordinates the Italian Network for the promotion of folic acid use in the primary prevention of congenital anomalies [42]. The network is composed of more than 200 public and private organisations, including local health authorities, patients associations, scientific societies, research institutes and communication

experts. It delivered a “Recommendation for the peri-conceptional use of folic acid” and is currently working towards the broad implementation of this recommendation. Moreover, CNMR is member of the ESCO group on “Analysis of risks and benefits of fortification of food with folic acid” at EFSA (ESCO Report on Analysis of Risks and Benefits of Fortification of Food with Folic Acid (www.efsa.europa.eu/en/scdocs/doc/3e.pdf) and www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902253891.htm) [43, 44];

- *epidemiological information.* In collaboration with the regional registries of rare diseases, CNMR runs the National Register of Rare Diseases, which collects epidemiological information that assists in determining the dimensions of the issue and potential risk factors, as well as supports clinical research and the definition of diagnostic criteria;
- *orphan drugs.* CNMR has established the National Register of Orphan Drugs, that contains data on the diagnosis and follow-up of the patients treated with orphan medicinal products authorized at a centralized level by the EMA and reimbursed by the Italian National Health Service (NHS). The web based Register, managed jointly with the Italian Agency for the Medicinal Products, is for post marketing surveillance. It allows centres prescribing a specific orphan medicinal product to request on line the credentials to access the register and collect information about the prescription, the dosage and relevant side effects. There is an established time interval for mandatory follow-up. These drugs are supplied to the patients via hospital and territorial pharmacies that must check in the register the amount of medication given to the patients. The software also performs some statistical analysis automatically. Obviously, all the registries work in accordance with the laws and regulation regarding the protection of personal data (Legislative Decree 196/2003 and others);
- *coding of rare diseases.* CNMR coordinates a national platform (experts, minister of Health, regions) for the improvement of the rare diseases coding process and contributes to the classification and coding of rare diseases for the preparation of WHO ICD-11, in collaboration with the EUCERD;
- *continuing education and training for health professionals; patients' and families' empowerment.* CNMR is developing a program of continuing education

in rare diseases addressed to GPs and other health professionals. CNMR has been carrying out, in collaboration with the Italian National Council of rare diseases Patients' Associations, a number of courses, addressed to Patients' Groups, aiming at empowering patients, as well as their families, in the daily management of their disease. In addition, CNMR organises several Congresses, Workshops and Meetings on general topics and specific themes [45];

- *information and communication on rare diseases.* CNMR holds a portal on rare diseases (www.iss.it/cnrmr) which provides information of interest to rare diseases patients and includes a user friendly tool for searching disease-specific information. The free toll telephone number (800-896949), while complementing the information offered by the web site, ensures a more direct psychological counseling of the patients and provides expert answers to specific questions and needs. A CNMR Newsletter on rare diseases and orphan drugs, providing information on ongoing research and public health activities on rare diseases, is regularly published by ISS;
- *narrative-based medicine.* CNMR launched, in collaboration with a number of patients' associations, the project “Rare diseases and narrative-based medicine”. This project aims at reducing social exclusion of rare diseases patients and at promoting their participation in society. To facilitate patients in telling their own personal experience of the disease and to bring their stories to light so that they can be shared with the rest of society, raising awareness and reducing the barrier towards diversity and the unknown, a public contest of fine arts and literary works was organized for the first time in 2009 and since then renewed. More than 300 fine arts and literary works are submitted to this competition, named “Il Volo di Pegaso” (The Flight of Pegasus). The best pieces are selected by a jury made up of literary and art critics and awarded a prize during a public ceremony held at the ISS during the European/International Rare Disease Day, which is gaining wide resonance and appreciation.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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