Presidenza del Consiglio dei Ministri

ORPHAN DRUGS FOR PERSONS AFFECTED BY RARE DISEASES

25th of November 2011

INDEX

Presentation

The document “Orphan drugs for persons affected by rare diseases” describes the difficulties faced by people affected by rare diseases which still pose a challenge as regards diagnosis, the limitations of aid and therapy, which, in most cases, is non-existent. The text focuses on the statistical data currently available regarding rare diseases and orphan drugs on a national and international level, in order to highlight the problematicity of the issue also on a bioethical level.

The rarity of the disease does not, in actual fact, allow for investment by pharmaceutical industries, on account of the scarcity of economic returns. The problem can not be tackled only nationally but must also encompass a European and international dimension.

The NBC, while recognizing the difficult solution of the problem, proposes some measures in order to limit it and ensure - as far as possible - the conditions of justice; promotion and economic support of research, by public and private structures, for a better knowledge of rare diseases, and the development of orphan drugs; the careful control of expenditure so as to avoid wasting resources or speculation; greater coordination in the search for genetic abnormalities with the appropriate development of genetic counseling and genetic therapies; the reduction of the threshold that defines the rarity of disease to ensure the sustainable promotion of research, development, and the marketing and delivery of truly innovative drugs.

In addition, request is also made to provide aid for families, as often these are diseases that affect children. It is also recommended that a European fund be created to support the discovery of diagnostic tools and new drugs by giving impulse to trials (both international and multi-centre trials), in full respect of the ethical rules. Finally, it highlights the need to consider orphan drugs for rare diseases a priority in the research programmes of public bodies, *charities* and private individuals.

The document was prepared by Prof. Silvio Garattini, with the collaboration of Profs. Salvatore Amato, Adriano Bompiani, Antonio Da Re, Bruno Dallapiccola, Marianna Gensabella, Laura Guidoni, Laura Palazzani, Monica Toraldo di Francia, Grazia Zuffa, together with the members of the working group Profs. Luisella Battaglia, Maria Luisa Di Pietro, Carlo Flamigni, Assunta Morresi, Andrea Nicolussi, Giancarlo Umani Ronchi.

The opinion was approved by those present: Profs. Salvatore Amato, Luisella Battaglia, Stefano Canestrari, Francesco D’Agostino, Bruno Dallapiccola, Antonio Da Re, Lorenzo d’Avack, Riccardo Di Segni, Carlo Flamigni, Silvio Garattini, Marianna Gensabella, Assunta Morresi, Andrea Nicolussi, Laura Palazzani, Vittorio Possenti, Rodolfo Proietti, Monica Toraldo di Francia, Giancarlo Umani Ronchi, Grazia Zuffa. Prof. Demetrio Neri expressed his negative vote. Profs. Adriano Bompiani, Roberto Colombo, Maria Luisa Di Pietro, Romano Forleo, Laura Guidoni, absent at the session, subsequently expressed their assent Prof. Cinzia Caporale outlined her non-adherence to the document.

The President

Prof. Francesco Paolo Casavola

Introduction

When one speaks of rare diseases we refer to a large and heterogeneous group of pathologies characterized by a low rate of frequency in the population[1], whose criterion of classification is in general purely epidemiological. Not well known and poorly researched, these diseases often have a chronic and debilitating outcome, and/or premature mortality, they strike in general and considering only the population of Europe, roughly 30 million people, half of these develop the disease already at the age of childhood. As regards the scope of the term rare disease, in Europe, "the entity of rare disease appears as a concept of a health and social nature, thereby meaning not only the diagnostic and therapeutic aspects, but also those inherent to activities of prevention, rehabilitation and socio-economic support"[2].

From a regulatory perspective, the first public recognition of the importance of the problem of rare diseases, dates back to the 80's of last century, and this coincides with the launch in 1983, of the National Organization for Rare Diseases and the simultaneous enactment, always in the U.S., of a specific law on `orphan` drugs (Orphan drugs Act). In the 90's the European Union too began to study the problem, so that in 1999 orphan diseases were identified as a priority area for Community action in the context of public health (Decision no. 1295/1999/EC of the European Parliament and Council). With this decision, the Union's aims: to improve access to information, to stimulate the training and retraining of health workers, to promote transnational collaboration of voluntary and professional associations and, together, the epidemiological surveillance of rare diseases and the creation of a network of experts. In 2000 the Regulation of the European Parliament and the Council on orphan drugs was drawn up (Regulation n.141/2000) - establishing a Community procedure for the designation of orphan drugs by establishing incentives for research, development and the placing on the market of those products – this was followed by a series of initiatives aimed at implementing the points of the program. In this way an increasing role is recognised to the contribution of knowledge and proactive activity given by the

[1] In Europe, the threshold is less than 5/10.000 (Regulation (EC) No. 141/2000).

[2] Cf. D. Taruscio, Rare diseases as an example of contrasting marginality, in "Rivista delle Politiche sociali", 2004, 4. In Regulation (EC) No. 141/2000 rare disease is defined as a: "a 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". These criteria, which refer to other factors, additional to the mere epidemiological criteria, are not adopted by other countries with different organisation of health care from the European ones, e.g. in the U.S. the recognition of rare disease is dependant exclusively on prevalence. It should also be noted that even in epidemiology there is an absence of uniformity in the definition of rare disease, the established threshold for inclusion as a rare disease may vary, depending on the country and the relevant legislation, and that the same prevalence criterion is not always certain, given the objective difficulty, for many diseases, to be diagnosed and consequently that cases be detected.

patients' organisations[3], reiterating the `added value` derived, in the complex field of rare diseases, from the coordination of action on a European level as well as transnational collaboration. As regards this aspect, there are at least two initiatives among the most recent to be reported: the 2009 Recommendation of the Council of the European Union, which called on Member States to adopt, by 2013, national plans and strategies for rare diseases, to identify centers of excellence and to promote participation in networks of European experts; the Directive of March 2011, concerning the implementation of patients' rights in cross-border healthcare[4], which "supports Member States in developing reference networks of healthcare providers and centers of excellence, especially in the field of rare diseases" (Art. 12), "in particular in order to make health professionals aware of the tools available to them at Union level to help them make a correct diagnosis of rare diseases" and "making patients, health professionals and agencies responsible for financing health care aware of the possibilities offered by the (EC) Regulation n. 883/2004 for the transfer of patients with rare diseases to other Member States, for diagnosis and treatments that are not available in the Member State of affiliation "(Art. 13).

As regards Italy, even though in the last decade several measures have been taken to for the setting up of suitable structures to the dictates of the community and in order to improve the condition of patients suffering from rare diseases, the legislative reference point remains the Ministerial Decree of 2001 (DM 279/2001), which regulates the establishment of the national network for rare diseases and gives the list of rare diseases for which there is recognition of the right to be entitled to exemption from participation in the costs related to health care[5].

It should however be noted that despite growing awareness in recent years towards the issue of orphan diseases, their lack of individual epidemiological importance makes them to this day still not very appealing for industries, that are not encouraged to seek and develop remedies that would not find an adequately remunerative market. On the other hand, when available, these treatments are very expensive, despite the fact that, in most cases, their efficacy and safety has not been sufficiently documented. For these reasons, orphan interventions are often less efficient than the more simple and less expensive ones, of sure - even if sometimes limited - efficacy, which are used on larger populations of patients.

The NBC believes, however, that the latter consideration, mainly based on the criterion of cost-effectiveness, and directed at protecting public health, can not

[3] The most important European organization, which has had a leading role in the dialogue with the European Commission as well as the promotion of national plans and strategies in favor of rare diseases, is Eurordis (European Organization for Rare Diseases); established in 1997, today it is the reference point of more than 500 associations of patients affected by rare diseases. Eurordis, among its many initiatives, also organizes an annual International Day of Rare Diseases (February 28th), with the aim "to raise public awareness, the European health authorities, national and local, and the political authorities, health professionals, researchers, academics, pharmaceutical and biotechnology industries and the media "on the issue of rare diseases. In 2011, the day had as its motto "Rare but Equal". With an emphasis on health inequalities in Europe and within individual states, while for 2012 the chosen theme is solidarity. See:
(http://www.eurordis.org/it/content/giornata-delle-malattie-rare-2011-focus-disparita-sanitarie).

[4] 2011/24/UE Directive of the European Parliament and Council of 9th March 2011.

[5] For the situation of rare diseases in Italy, see the Istisan Report 11/20. The National Registry and Regional/Interregional Registers of rare diseases The 2011 Report.

and should not be detached from a specific attention to the suffering of people affected by rare diseases and to a united commitment to the promotion of their health status.

The NBC has already examined, in the opinion on Drug experimentation (1992), the economic problems faced by pharmaceutical companies in the study and production of orphan drugs for rare diseases, hoping, however, on the basis of ethics that transcend the mere logic of economics, that orphan drugs may be `adopted`[6].

The patient suffering from a rare disease is primarily a person who has the right to health care: the right that, in this case, is expressed as a right to receive treatments with proven efficacy but also as a right to hope in the development of possible new treatments thanks to advances in pharmacological research. The two rights are implicit in the Preamble of the Constitution of the World Health Organization (WHO), which states that "the possession of better health that you are able to achieve is a fundamental right of every human being.

As noted by NBC in the opinion bioethical guidelines for equity in health (2001), there is introduced here the notion of "possible health" which opens, among other things, "one of the major issues of health justice, namely the 'impossibility of deciding matters concerning distribution, allocating to everyone the same amount of resources. Such a solution does not take account of the tension introduced in the health field from different natural and social distribution of disease and psychophysical deficits, and therefore the different degrees of intervention necessary to ensure possible public health"[7].

One should add that in the context of the difficult and sometimes tragic choices[8] imposed by the scarcity of health resources, it often happens that the person suffering from a rare disease feels even more emarginated, if not abandoned, for several reasons: on account of the many difficulties encountered regarding health care and because of the lack of real hope, in the near future, in the possibility of availability of effective treatment for their disease, which, due to its very rarity, is in actual fact neglected.

In addition, the research, development, and marketing of therapeutically effective drugs would seem to require investment on behalf of society of such magnitude as to be perceived as contrary to the interests and the right to health care of all other citizens suffering from common diseases. However, in a just society, an appropriate resolution should be found to solve this contrast. In order to deal with distributional issues related to health, there must be a justified and shared policy, for the allocation of resources which does not penalise any type of patients.

This NBC document intends to consider the problems raised by rare diseases and by orphan drugs in particular, for those who govern intervention and spending within public health care.

[6] A recent ruling by the Swiss Federal Court (23 November 2010) sets a limit on the management of certain drugs. (http://www.tsr.ch/emissions/36-9/3264987-trop-cher-tu-meurs.html).
[7] NBC Bioethical guidelines for equity in health, 2001.
[8] G. Calabresi, P. Bobbitt, Tragic choices (1978), tr. it. Scelte tragiche, Milan 1986.

Rare diseases: on the patients' side

Rare diseases raise a number of problems, both for the person who is affected, often burdened by serious or extremely serious disability, both for the family, and for the community.

The problems of the individual and the family concern mainly:

- the difficulty, or the impossibility, to access the correct diagnosis - due to the absence of identification of a clinical reference centre specialized in the pathology in question - with the consequent worsening of the patient's psychological condition and state of health;
- the delay in diagnosis adversely affects prognosis;
- the isolation and lack of scientific knowledge and information about both the disease, as well as existing laws and rights;
- the lack of adequate medical care and the necessary rehabilitative and psychological therapy, considering the chronic and debilitating nature of the majority of rare diseases and the disruption and destabilization that experience of the disease entails for the patient and family;
- the difficulty of access to treatment and care, that concerns both the obtainability-availability of innovative drugs, at a high or very high price, used specifically for a particular rare disease and already marketed in Europe as well as, when there are no specific etiological therapies, and the access to other treatment options;
- the strong inequalities that exist at regional and local level, in the access to diagnosis, to innovative therapies and, more generally, health care and social services;
- the high costs of treatment, overall, and the lack of support measures that meet the needs of daily and ongoing assistance determined by the disease, this burden falls almost entirely on the family, and often causes its impoverishment and exclusion from the world of work;
- the precarious conditions, that are often serious or very serious, of those affected, even after having obtained diagnosis;
- the heavy social consequences for the patient (stigmatisation, isolation at school and occupational activities, the difficulty of building a network of social relations).

A study sponsored by Eurordis (Rare Disease Europe[9]) has identified a number of problems related to the diagnosis of rare diseases:

- 25% of patients wait 5-30 years to obtain confirmation of the diagnosis;
- 40% initially receive an incorrect diagnosis;
- 25% must move to other regions in order to obtain diagnosis;
- in 33% of cases the diagnosis is communicated in an unsatisfactory way (12% in an unacceptable manner);
- in 25% of cases it is not reported to patients or their families that it is a genetic disease;
- Genetic counseling is offered in only 50% of cases.

[9] http://www.eurordis.org. The Voice of 12.000 Patients, 2009.

Besides all this, the *Dossier on the subject of rare diseases 2008*[10] (by Cittadinanzattiva, Tribunal for Patients' Rights, National Coordination of associations of the chronically ill), in pointing out the difficulties in actually enjoy the benefits provided by law and the considerable differences that exist between regions, states that over 40% of patients do not often have access to essential drugs, or drugs for the treatment of complications. Even more serious is the difficulty in taking advantage of innovative drugs. To overcome these difficulties several measures were proposed including the simplification in the marketing of to drugs for the treatment of rare diseases, for example by reducing, the time for publication in the Official Journal, a more rapid implementation on national territory, of the decisions taken at European level, effective and timely availability after the approval of the AIFA. Cost and inconvenience lead to renunciation to medical care by 1 out of 4 patients to which there should be added a further 37% for those who abandon due to bureaucratic impediments[11].

Other studies have found, that 57.9% of patients are forced to personally bear the costs of therapy with an annual cost that ranges from a minimum of 800 Euros to a maximum of 7,000 Euros and this leads to renunciation to medical care by 1 out of 4 patients to which there should be added a further 37% for those who abandon due to bureaucratic impediments (2008 study by the Tribunal for patients' Rights[12]); that for many parents to meet their care needs means to worsen their work situation, or to interrupt it completely (Pilot Study ISFOL[13]); Among the families participating in the study many live on a very low income, 35.1% are below the poverty level, or at high risk of poverty; almost 20% are forced to resort to loans, to cope with management of the disease.

Rare diseases: on the community's side

Rare diseases affect a limited number of people individually. In relation to the different definitions used, each of them affects less than 1 person in every 2,000 in Europe, 1/1.250 in the United States, 1/2.500 in Japan, 1/15.000 in Australia. The following are some examples:

Rare diseases with the highest estimated prevalence	
	Estimated prevalence per 100,000[14]

[10] http://www.cittadinanzattiva.it/files/approfondimenti/salute/malattie_croniche_rare/dossier_tema_malattie_rare_nov_2008.pdf.

[11] Il Sole 24 ore "Focus sanità", 11-17 November 2008, p. 14.

[12] http://www.cittadinanzattiva.it/files/approfondimenti/salute/malattie_croniche_rare/dossier_tema_malattie_rare_nov_2008.pdf.

[13] A. Spagnolo, difficult to to stay afloat. The needs of families and patients affected by rare diseases: a pilot study IAS, "About Pharma", 1/March 2011, p. 35 ff.

[14] Prevalence of rare diseases: bibliographic data, Orphanet Reporter Series. www.orphanet, May 2011, Number 1 and Number 2.

Brugada syndrome	50
Erythropoietic protoporphyria	50
Guillain-Barré syndrome	47
Familial melanoma	46
Genetic Autism	45
Tetralogy of Fallot	45
Scleroderma	42
Transposition of the great vessels	32,5
Focal dystonia	30
Marfan syndrome	30
Malignant non-Hodgkin's lymphoma	30
Retinitis pigmentosa	27,5
Narcolepsy	26
Multiple Myeloma	26
Alpha 1-antitrypsin deficiency	25
Congenital diaphragmatic hernia	25
Juvenile idiopathic arthritis	25
Neurofibromatosis type 1	25
Esophageal atresia	25
Polycythemia vera	25
Source: "Lancet", 2008	

However, the number of these diseases is very high (at least 6,000 according to the WHO). Consequently, the total number of patients suffering from rare diseases is enormous: an estimated 30 million in Europe, of which there are about over 1 million in Italy (although the absence of comprehensive data on the population of the rare patients makes it difficult to make a precise estimate), 25 million in the USA.

The treatments available for rare diseases vary in kind and are not restricted only to pharmacological treatments[15]. This document, however, refers exclusively to pharmacological treatments.

Overview of rare diseases activities in Europe and key developments in 2010. Joint Action to Support the Scientific Secretariat of Rare Diseases Task Force, European Union Commission of Experts on Rare Diseases, 20082291.

[15] See the following table:

Examples of treatments available for rare diseases
• Limitation of a substrate in the diet (eg. Phenylalanine in phenylketonuria) • Elimination of drugs (eg. Barbiturates in porphyria) • Gene therapy (eg. In adenosine deaminase deficiency) • Transplants (eg. Marrow in thalassemia; liver in biliary atresia, heart in dilated cardiomyopathy, etc.)

Since 2000 (Regulation (EC) No 141/2000[16]) to 2010, there have been approved in Europe little more than 60 orphan drugs that treat around forty rare diseases. If we consider the availability of orphan drugs for disease groups, the most available are those for metabolic diseases (64%) and rare tumors (59%), while there is a lower availability in other fields such as, for example. cardiology, neurology or hematology, and it is the drugs that treat the rarest of conditions that are not available.

It should be stressed however that, given the few approved drugs, there are over 800 products designated by the regulatory authority (COMP) as potential orphan drugs. These products are not developed because of lack of funds. Hence the necessity of establishing an appropriate European fund for translational research on orphan drugs, privileging research for the rarest of conditions.

According to the Italian Drug Agency (AIFA), the use of these drugs in 2010 amounted to 6,839,423 DDD (daily doses) for a cost of 661,709,750 Euros.

Instruments to meet needs and limit their impact

The picture briefly represented here renders the idea of the size of two problems: the first is the disparity between needs and their satisfaction, that is, between the number of rare diseases and the people affected by them and the number of genuinely effective treatments available; the second is the current and future burden arising from this problem, and therefore the need to promote research and development of orphan drugs and, thereafter, to make them available to patients.

Several international initiatives seek to provide a solution to these problems. The International Rare Disease Research Consortium (IRDiRC[17]), for example there is the ambitious project to develop, by 2020, 200 new therapies for rare diseases and diagnostic tests for all rare genetic diseases, together with advisory and family support programmes.

- Removal of pathological tissues (eg. Neurofibromas in NF1; colectomy in familial polyposis of the colon)
- Reparative surgery (e.g. Congenital heart disease)
- Neuropsicomotoria therapy (eg. Various types of psychomotor retardation)
- Prostheses (e.g. Deafness, intracerebral electrodes in dystonia)
- Robotics (eg. Exoskeleton for deambulation in diplegia)

[16] Data were collected by Eurordis and the National Federation of Rare Diseases (UNIAMO), starting in September 2010, the survey, which examined the question of access to 60 orphan drugs with marketing authorization in Europe, has shown that it is precisely the drugs that treat the rarest of conditions that are not available
http://www.uniamo.org/it/news/news-europa/190-indagine-eurordis-sullaccesso-ai-farmaci-orfani-in-europa.html.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF.

[17] http://www.geneticalliance.org/irdirc.

Instruments to measure the effectiveness and efficiency of intervention

Two problems of great importance concerning the choice of the resources to be allocated for the treatment of rare diseases, regard the effectiveness and efficiency of these interventions and the possibility of their measurement[18]. The QALY (Quality-Adjusted Life-Year) is the most common instruments used to determine the value of a drug. The QALY measures the survival and quality of life of the patient in reference to a treatment. For example, a vaccine used at a pediatric age, which prevents death or ensure decades of life without that disease, is credited with many QALYs, an anticancer drug, which allows increased survival of just a few weeks, moreover, burdened by a poor quality of the remaining life, will have a very modest QALY. The cost of treatment, in relation to the QALY, represents, in general, a measure of cost-effectiveness to determine the value for money of one intervention in relation to another.

In a system with fixed financial resources (each year a budget for health spending is established, with a set percentage cap for drug expenditure) the cost for QALY could in future be the instrument by which the choice of priority intervention is determined: in the context of forecast expenditure only the most efficient interventions are reimbursed. This would make it possible to purchase more public health with the available budget.

The criterion of QALY, however, is not free from critical consideration, in general and especially when it comes to rare diseases It is purely statistical, which leads to a single social factor in the evaluation of a specific health intervention spread across multiple subjects, based on an overall calculation that does not take into account the different conditions of the people involved. It should be emphasized that QALY should not be the physician's clinical reference, as it is a tool for the allocation of resources. Its application, as an exclusive criterion therefore, runs the risk of not meeting up to the requirements of fairness in the allocation of scarce resources based merely on a question of efficiency.

Although a criterion of efficiency such as the one based on the cost/effectiveness of interventions, ensures an efficient allocation of resources for the purchasing of the greatest possible amount of public health, it does not promise to adequately safeguard the individual rights and needs of marginal patients', consequently, additional or alternative instruments of policy must be identified in order to meet them. Therefore, the (ideal) primary objective to achieve must be the improvement of standards and the quality of life for every patient, without discrimination based on the nature of the disease or the cost of therapy. All the energies of researchers, health professionals and those who manage the public health, supported by the actual patients' associations should be directed towards this aim. Therefore, the NBC maintains reflection on this debate open to contributions from new evaluation criteria.

[18] As already noted by the NBC the search for just and shared policies in selecting priorities "requires the assignation of a higher value to the criteria of quality and effectiveness of medical services".

Sustainability of pharmaceutical expenditure

Except in rare cases of clear disproportion between the cost and effectiveness, the Italian National Health Service has for now guaranteed to cover not only interventions at low cost and high yield (think of a few tens of Euros for vaccines administered in childhood, allowing decades of life of a good quality), but also interventions at a very high cost and modest yield (e.g. the tens of thousands of Euros paid for innovative medicines that lengthen only by a few weeks the life of cancer patients in the terminal stage).

Some worrying signs (such as the exceeding in 2010 of the cap of hospital pharmaceutical expenditure) are the signal of an imminent breakdown in the balance maintained for years by a careful policy of management of drugs and their prices Consequently, there could be in the future, a change of choice, mortifying for the right to health of certain groups of patients, contrasting with the ethical and legal principles that inspired our Constitution (equality, solidarity, personal development, the right to health).

The case of orphan drugs

Orphan drugs - generally, very expensive, and to date reimbursed on the basis of different criteria from that of cost effectiveness - could be affected by the above-mentioned situation. As well as being expensive, they often have little documentation regarding their actual clinical effectiveness[19].

Orphan drugs and their approximate cost		
Drug	Rare disease	Cost/patient/year (Euro)
Imiglucerase	Gaucher disease type 1	104,000 [a]
Alfa-agalsidase	Fabry disease	145,500 [a]
Idursulfase	Mucopolysaccharidosis	462,500 [b]
Afa alglucosidase	Pompe disease	300,000 [a]
Sapropterin	phenylketonuria	115,000 [a]
Eculizumab	Paroxysmal nocturnal hemoglobinuria	280,000

[19] An example is the demonstration of the modification of the biochemical parameters in the short term, such as glycolipids in Fabry disease the Insulin-like growth factor-1 in acromegaly, glycosaminoglycans in the mucopolysaccharidoses, etc. is not sufficient to ensure a greater and/or better survival in the long term (Joppi et al. "Br J. Clin. Pharmacol." 2006 and 2008).

Cost calculated using unit prices obtained by the British National Formulary UK for such patients and, where necessary, according to body weight: a 70 kg b 48 kg Exchange rate sterling/Euro used:: 1,1192 (28.06.2011)
Source, “British Medical Journal”, 2010

The uncertainty regarding the real clinical efficacy of some orphan drugs and the limited capacity of the system to ensure free availability for the patients affected by rare diseases could lead to restrictions on the reimbursement of drugs and/or the accentuation of the already ongoing trend, for policies and measures to differ from region to region, and consequently, for some patients, there is non-recognition of the equal right to treatment of the disease and their being treated in a discriminatory manner depending on the location[20].

At the same time it is unthinkable that a gradation of interventions, based on an evaluation of the cost-effectiveness, can be completely set aside for orphan drugs: investing too high a share of resources to make available more and more drugs for rare diseases would considerably decrease the quota allocated to the treatment of diseases that are not rare. Therefore, it is necessary to address the problem of the choice of distribution criteria for scarce resources, such as those of their health system, without opposing the protection of public health to the right to treatment of the 'disadvantaged', such as those suffering from rare diseases.

A Question of Justice

The basic ethical question concerns the possibility of identifying univocal and transversely valid criteria in order to guarantee fairness in meeting the needs of the individual and the community in the distribution of public resources.

It is evident that the limited resources available in health care make it impossible to have a model of justice capable of guaranteeing "everything to everyone", although, as already noted by the NBC in an earlier opinion, we must strive - at least in principle - to ensure "all that is effective for all those in need", as each patient has the right to be treated equally, regardless of solely economic calculations. This is a postulate (equal consideration being due to every person) which is the reference point for any reflection in this area.

In addition, it should not be forgotten that a fair distribution of resources, in order to be so, must take into account also difference. The lack of consideration of individual differences can in fact produce profoundly anti-egalitarian effects and this for the obvious reason that the equal consideration of everyone may entail 'unequal' treatment in favour of those who are in a disadvantaged position. It is

[20] On policies and measures that differ from region to region, cf. I. Ciancaloni Bartoli, Regions in random order, in "About Pharma '1/marzo/2011, p. 33 ff. and, in the same issue of the journal, A.Spagnolo, hard to stay afloat. The needs of families and patients affected by rare diseases: a pilot study IAS, cit.; See also Cergas-Bocconi, Analysis of regional policies on access to innovative drugs, the final research report, September 2008 http://www.celgene.com/downloads/SINTESI_RAPPORTO_BOCCONI.pdf.

therefore necessary to ensure justice while respecting the equality of human beings regardless of the existential conditions (e.g. the disease or incidence of the disease) and - at the same time - the different needs of each, relating in this case to the different states of health/disease. It is precisely this interpretation of the concept of justice which is at the basis of equity. It follows, as noted in the introduction, that, in the face of health issues, a distribution policy should be found - moving from the concreteness of human reality - offering to all individuals an equal opportunity to achieve their full health potential permitted by their condition[21].

Following this ideal regulative principle, although not hiding the difficulties, the NBC believes it possible to search for a solution, albeit partial, to a very real problem.

Resolutions aimed at limiting the problem

The guidelines for the protection of the right to treatment of people suffering from rare diseases also include measures to restrict the size of the problem. Possible areas of intervention include:

- The promotion and economic support of both research aimed at achieving a better understanding of rare diseases and the causes of their occurrence (under the label of a specific syndrome, e.g. very different diseases, that share similar symptomatologies, whose cause is still not known, could be grouped together), as well as research and development of orphan drugs, enhancing the contribution of numerous patient associations especially active in this area. Currently there are about 800 active ingredients that have received orphan drug designation, but which can not be developed due to the lack of economic resources. More specifically, a European (or even international) fund should be established, for the creation of orphan drugs, to draw attention to the problem on behalf of the national health policies, and to encourage private investment in this sector using appropriate strategies.

- Close monitoring of expenditure on orphan drugs, in order to avoid wasting resources. A drug originally recognized as an orphan drug should not be considered as such when alongside the indication for this rare disease there are added other indications for common diseases. The cost, sustainable for a niche area, should not remain the same for interventions which apply to large populations[22] Therefore a cap must be imposed on expenditure for these drugs, so as to ensure an adequate return on investment for research and development, but also in order to avoid speculation by virtue of the fact that the market in gradual expansion does not affect the initial price of the product[23] Indeed often certain drugs that have been designated as orphan drugs and, as such, authorized for sale, may subsequently be clinically developed also in other pathological areas and obtain for these new clinical indications, marketing authorization. The price

[21] See the aforementioned NBC opinion, Bioethical guidelines for equal access to healthcare.
[22] N. Hawkes, D. Cohen, What makes an orphan drug?, “BMJ”, 2010, p. 341, c6459.
[23] For example, imatinib is an orphan drug, but it requires an investment of 145 million Euros only in Italy.

agreed upon with the drug regulatory authority for an initially restricted market, in these cases, is applied to trade on a large scale, with a heavy cost burden for the NHS.

- The promotion of research directed at ensuring clinical effectiveness and quality control of orphan drugs, when addressed to neglected areas, benefit from concessions and privileges. They should offer real benefits to patients, that are certain and measurable in terms of increased survival and/or better quality of life. Today, this rarely happens[24]. It is important to encourage international multicentre experimental research to overcome the problem of the scarcity of patients and facilitate the planning of alternative designs for clinical trials[25]. In this respect, it is required that Governments put pressure on the European Commission and on the European Regulatory Agency (EMEA, European Medicines Agency) in order to increase the rigour in the evaluation of new drugs, and particularly orphan drugs, so they respond better to the needs of patients and the NHS.

- A more coordinated investment:: for research of genetic anomalies and their markers, in the development of diagnostic tests, the pharmacological treatment of inherited rare diseases, in the formation of medical, nursing and laboratory expertise, to transfer and make available the new knowledge. In fact about 80% of rare diseases have a genetic origin and the number of conditions for which genetic tests can be performed is constantly increasing (about 100 in 1993, over 2,200 in 2010, GeneTests database). These developments have not been matched by the number of adequate facilities for genetic counselling and appropriate pharmacological therapies[26].

- The reduction of the threshold that defines the rarity of a disease (currently 1/2.000 in Europe) to ensure a sustainable promotion of research, development, marketing and delivery of truly innovative drugs. It is important to introduce serious reflection on the possible reduction of the threshold considering the consequences that this might entail. The threshold to be adopt should be sufficient to define a market situation capable of ensuring to industries - without reducing patient protection - satisfactory economic returns, and the promotion of their commitment to the research and development of effective orphan drugs. For example, if a prevalence of 0.5/10 000 (that is 5/100.000) were adopted, instead of the current 5/10.000, the industry would however still have a potential market of about 25,000 patients for that rare disease in the EU. This is an area of action of a significant size, especially in consideration of the chronicity of the majority of these treatments. n fact, assuming a drug cost that is even much lower than average for the present effective orphan drugs, for example, 6,000 Euros/patient/year, there would be an annual turnover of 150 million for the EU alone, therefore able to guarantee to pharmaceutical companies significant economic returns. The high prices of orphan drugs, however, allow for, higher revenues than those prefigured

[24] See: Joppi et al., "Br J. Clin. Pharmacol. "2006 and 2008.

[25] S. Gupta, M.E. Faughnan, G.A. Tomlinson A. M. Bayoumi, A framework for applying unfamiliar trial designs in studies of rare diseases, "Journal of Clinical Epidemiology", 2011, pp. 1-10.

[26] This document does not intend to address the question of the use of genetic tests in the prenatal sphere; the document only deals with the issues of those already born and suffering from a rare disease.

here, even for diseases that are even rarer than those identified by the above-mentioned threshold[27].

Obviously the new threshold applies only to the use of the European fund for the development of orphan drugs and does not affect the social care providence carried out in various European countries including Italy.

The NBC Guidelines

Pending further contributions on the identification of appropriate assessment criteria, the NBC reiterates that, particularly in the case of rare diseases, the right to health care for people affected by rare diseases can not be called into question by the contraction of economic resources and choices of allocation of funds driven by the sole criterion of cost-effectiveness. However, being aware of the scale the financial commitment required by research and therapy in the context of rare diseases and the difficulty that this commitment creates in the choice of priorities that guarantee the right to health for all, the NBC suggests adoption of certain measures able to limit the onus. These measures are general measures and guidelines of principle, which do not allow us to propose concrete solutions, that are specific and immediate, but they delineate the reference values for health policy choices in this area. These measures include in brief:

1. the recommendation, to the European and national legislators, to adopt a new definition of rare disease, based on more restrictive epidemiological criteria, and to establish a cap on the revenues for orphan drugs, over which to revoke the designation of orphan drug and their privileges and incentives in order to discourage speculative policies based on the extension of the clinical indications of very expensive products;

2. the promotion taking charge and treatment, pharmacological and non pharmacological, of rare diseases, both hereditary and non-hereditary even reducing the number of undiagnosed cases, reducing the time of diagnosis and increasing the availability of genetic counselling for hereditary diseases;

3. the promotion of clinical trials on a multicentric, national and international level, in full respect of the subjects on which the testing is done (children or other conditions of particular vulnerability) and the criteria of ethics (informed consent, confidentiality of information, etc…); for this purpose the establishment of a European fund for the translational research of new orphan drugs is advocated;

4. the promotion of the transfer of research results in the treatment of rare diseases and the simultaneous adoption of more rigorous criteria for assessing the

[27] For example, at a cost of more than 50,000 Euros per year per patient agalsidase for Fabry disease, which has a prevalence of 1/40.000, would have a market well in excess of 600 million Euros in Europe. Imiglucerase for Gaucher's disease (prevalence of 1/30.000) costs about 230,000 Euros per year for each of the over 16,000 patients in the EU, a potential market of approximately 3,800 million Euros.

degree of innovation of orphan drugs before they are placed on the market, ensuring the best national and international clinical practice to all patients, without exceptions or regional differences;

5. the monitoring of the effectiveness and tolerability of drugs granted for compassionate use or used in an off-label form;

6. the recovery of resources capable of sustaining the onus of orphan treatments through the redistribution of the burden of expenditure for some classes of drugs, that are widely used and low cost, by the NHS to patients, but also by promoting campaigns so that large companies, both pharmaceutical and producers of consumer goods, are encouraged to 'adopt' one or the other orphan diseases, considering that the 'ethics' of a product, once advertised, may represent an added value.

Appendices

Regulatory framework

The regulatory framework that sets the context of the problem is represented by certain fundamental references:

Art. 32 of the Constitution: The Republic safeguards health as a fundamental right of the individual and as a collective interest, and guarantees free medical care to the indigent.

Law 833, 23 December 1978 which established the National Health Service: The Republic safeguards health as a basic right and collective interest through the NHS. The protection of physical and mental health must respect the dignity and freedom of the human being. The NHS is made up from all the functions, facilities, services and activities intended for the promotion, maintenance and recovery of physical and mental health of the entire population without distinction of social or individual conditions and in a manner that will ensure the 'equality of citizens for the service.

Ministerial Decree 279, May 19, 2001 (Rules of establishment of the national network for rare diseases and exemption from participation in the cost of the related health care services): Article 3 National Register 1. In order to allow national and regional planning of interventions aimed at the protection of individuals affected by rare diseases and to undertake their surveillance, there is hereby established at the National Institute of Health, the National registry of rare diseases. 2. The Registry collects personal data, medical, clinical, instrumental, laboratory anamnesis and related aspects regarding risk factors and lifestyles of people with rare diseases, for study purposes and scientific research in the epidemiological, medical and biomedical fields. Article 6 Methods of the provision of services. 1. The patient eligible for exemption has the right to free health care, as prescribed in the manner envisaged by current legislation, included in the basic levels of health care, that is effective and appropriate for the treatment and monitoring of the disease he is affected by, in order to prevent a further worsening of the condition.

Other references at European level are:

- 23 Oct 2007 – Decision 1e350/2007/EC – 2nd Programme of Community Action in the field of Health (2008-2013) – Point 2.2.2. “Promote action on the prevention of rare disease”.
- 11 Nov 2008 – Communication COM(2008)679 to the European Parliament, the Council, the European Union Economic and Social committee of the Regions on Rare diseases.
- 30 Nov 2009 – Commission Decision (23009) 9181 – Establishment of EUCERD (European Union Commission of Experts on Rare Diseases).
- 2009 Report on Initiatives and incentives in the Field of Rare Diseases of the European Union Committee of Experts on Rare Diseases.

Glossary

CHMP: Committee for Human Medicinal Products, this committee evaluates the documentation supporting the request for authorisation to market human medicinal products, including orphan drugs. The CHMP assessment is summarized in the opinion which the European Commission takes into account before granting the definitive drug marketing authorisation for the EU market.

COMP: Committee for Orphan Medicinal Products, the committee is responsible for awarding the designation of the status of "orphan" drugs to developed drugs or to the development of drugs for the treatment of rare diseases, the designation is granted on the basis of the request made by a sponsor, meaning a person or company; designation is granted on the basis of epidemiological data (prevalence of the disease to be treated <5/10.000 inhabitants), the criteria of clinical plausibility and the potential benefit to the patients to be treated.

DDD: Defined Daily Dose the assumed average maintenance dose per day for a drug used for its main indication in adults.

Orphan drugs: are medicines that treat or cure rare diseases and, as such, are “orphans” in an extensive market, such as the market for drugs that treat highly prevalent diseases (real or supposed).

Rare diseases: according to European legislation, are diseases that have a prevalence of up to 5/10.000 inhabitants in the European Union.

Off label: with reference to what is foreseen in the Summary of Product Characteristics (SPC) of a registered drug approved by the Ministry of Health, the off-label use refers to its being prescribed in an non-compliant manner as regards disease, population or dosage (e.g. used differently to the therapeutic indications, means, and the expected method of administration, in different doses compared to those required by the SPC dosage, overriding the contraindications referred to in SPC, in contrast to the uses authorized by the Ministry of Health, and the list prepared by the National Drug Evaluation Board.

QUALY: Quality Adjusted Life Years is a unit of measure used in cost-utility analysis that combines duration and quality of life. It is used as an index weighting in the evaluation of increases in life expectancy related to health care. One QALY equal to 1 corresponds to life expectancy of one year in normal health; the value 0 corresponds to death. The measurement scale is continuous and to some years of life there can also be given values less than 1 in relation to a non-optimal quality of life or even negative values, in the case, for example, of a serious condition of immobility or acute pain.

Translational Research: Translational research is the pre-clinical biomolecular research that produces results that are quickly transferable to clinical activity and, vice versa, that clinical research proposes that in-depth insights and solutions be verified through basic testing. Research of a translational kind is, therefore, integration between experimental research and clinical practice. One example is pharmacogenomics, whose aim, in oncology, is to construct a genetic map of the tumors to obtain a predictive test to determine the response to therapy. More generally, translational research includes:

- The basic scientific studies which define the biological effects of treatments in humans;
- Investigations in humans that outline the biology of the disorder and provide the scientific foundation for the development or improvement of new therapies;
- Non-clinical studies or animal studies conducted to improve clinical therapy.

Clinical studies: experimental studies in humans which through successive stages aim to establish the pharmacokinetic properties of a drug (absorption, distribution, metabolism, excretion), its mechanism of action, effective and safe doses, tolerability, efficacy and safety. Phase I Study: conducted on a small group (a few dozen) of healthy volunteers (or patients who have no therapeutic options) to study pharmacokinetics, mechanism of action, ideal doses. Phase II studies: conducted on a larger group (several dozen or a few hundred) people, preferably patients, designed to confirm the active doses and to determine their effectiveness more often based on surrogate outcome measures (blood pressure levels, blood sugar, cholesterol levels, volume of a tumour, etc.). Phase III studies: conducted on hundreds or thousands of patients, are intended to establish the actual efficacy and safety of the drug through clinical outcome measures, that is, events that affect the duration and/or the quality of life of the patient (death, myocardial infarction, stroke, bone fracture, physical or mental disability, dependence on others, hospitalisation, etc.). Phase IV studies: conducted on large populations, when the drug has already been approved for the market, designed to establish the efficacy and safety in real conditions of use in clinical practice, or to evaluate specific aspects of toxicity revealed through time, or new clinical indications, or the risk-benefit profile of vulnerable population groups (pregnant women, children, the elderly, etc..) or combined with other drugs.