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JOINT VENTURE BY CREA Sanità & OSSERVATORIOMALATTIERARE

POSITION PAPER OSSFOR

EARLY ACCESS PROGRAMS: OUR PROPOSALS FOR IMPROVEMENT OF IMPLEMENTATION OF LEGISLATION ENFORCEMENT

ORPHAN DRUG OBSERVATORY OSSFOR

The Orphan Drug Observatory is the first research center and think-tank devoted entirely to the development of policies for governance and sustainability in the field of rare diseases. Born in 2016 as a joint initiative of the research center C.R.E.A. Health (Consortium for Economic Research Applied To Health) and the Observatory for Rare Diseases journal O.Ma.R. in order to systematize the existing information, fill the gap of knowledge and information about the sector, fostering an open and direct confrontation between institutions and key stakeholders.
The objective is to contribute a guarantee to rapid access for therapies and assistance for rare diseases, favouring a singery between the institutional, political, academic and business worlds, through a free dialogue useful to identify the best strategies to put in act. To this aim a continuative activity of research and monitoring is exercised and results in an Annual Report and a series of publications useful to disseminate, to a wide public, some themes of considerable importance.

The publications of OSSFOR—Reports, booklets, analyses, preparatory documents, organisational and normative proposals and every other comprehensive documentation – are made public through the publication on the website www.osservatoriofarmaciorfani.it
The Observatory is funded by an annual and unconditional support of the greatest number of companies engaged in research and development of orphan drugs. The extreme "fragmentation" of lenders is maximum guarantee of independence and impartiality with respect to donors themselves and towards institutions.

THIS DOCUMENT AND 'WAS REALIZED THANKS TO THE CONTRIBUTION OF NON-CONDITIONAL:

POSITION PAPER

Among the publications of OSSFOR are the Position Paper, and therefore documents which report the Observatory's position on the topics selected, researched and developed during the year. The OSSFOR position is the result of a debate that took place in the course of a year, between the institutions, representatives of companies and other individuals who in some way intervene in the procedures described in the regulations. The goal of OSSFOR is to identify, in the existing regulations, the critical points of application and identify possible improvements.
At the beginning of each year, OSSFOR, identifies the subject on which to base the study and research activities in order to articulate, at the end of the work, its position.

PREMISE

Orphan drugs, on the basis of Regulation (EC) n. 726/2004, have a mandatory centralised procedure, which foresees that EMA (European Medicines Agency) through its Committee for Human Medicinal Products or CHMP does a scientific evaluation of the documentaion presented by the applicant and issues an opinion that is communicated to the European Commission. The Commission issues a decision that is binding for all Member States.

Even today many rare diseases have no specific drug therapy with approved indications. For this latter reason, the Early Access Programs (EAPs) are a necessary resource because, in the absence of a viable therapeutic alternative, allow patients with severe and highly debilitating rare diseases to resort to treatments being tested or not yet authorized by the Italian State. The EAPs are programs that ensure ethical mechanisms and controlled access to experimental drugs outside of clinical trials space and before the commercial launch of the drug, to patients with serious diseases for which there are no other treatment options. The programs of access can be taken into consideration in the first phases of development of a product that shows promise for patients who cannot participate in clinical trials, due to insufficient criterie for eleggibility of protocol.
In Italy there are various regulations, not always developed specifically for orphan drugs and rare diseases, which, for various reasons, govern access to drugs off-label, or drugs not marketed in Italy.

Law no. 648/1996

The law in question, among other things, provides that if there is not a viable therapeutic alternative, the National Health Service (NHS) may provide at its own expense, after consultation with the Scientific Technical Commission (CTS) innovative medicines on the market in other States but not in Italy, medicinal products not yet authorized undergoing clinical trials and medicines to be used for a therapeutic indication other than the authorized.
Also, with the Article.3 L. n. 79/2014 the possibiity has been foreseen of delivering, in accordance with L. n. 648/1996, even in case of valid alternative therapy, medicines to be used for a therapeutic indication different from the authorized, provided that this information is known and subject to research in the medical and scientific community nationally and internationally, within the parameters of cost-effectiveness and appropriateness.
With the decision of 20 July 2000, the Ministerial Committee on Medicines, besides indicating the documentation for the request, specified that for inclusion in the list provided in accordance with L.648/1996, Phase II clinical trials are needed. Once on the list, medication may be prescribed.

Law no. 326/2003

Acccording to this legislation pharmaceutical companies are required to deposit, in a specific fund established by AIFA, a contribution equal to 5% of the self-certified expenses net of expenses for the personnel assigned.

The 50% of the above resources are destined to the constitution of a national fund for the use, charged to NHS, of orphan drugs for rare diseases and drugs that represent a hope of cure, awaiting the marketing, for particular and grave pathologies. The petitions of access to the fund are fowarded to AIFA by the Regions, Centres of reference that have patients in cure, or specialised structures indicated by the Regions and refer to conditions of the single patient.

The legislaton in question does not indicate specific prerequisites for the petition of access to the fund established by the law L. n. 326/2003; the single petitions are evaluated by AIFA in relation to the peculiarities of each single case.

METHOD

The study conducted by OSSFOR during its first year of activity concentrated on the legislation, the indications, in order to identify critical issues related to its application. The result of that study was subsequently object of debate with the stakeholders operating in the sector, during the Technical Discussions, participated by: EMA, AIFA, The State - Region Conference, Eupati – European Academny of Pazients, Uniamo – Italian Federation of Rare Diseases Onlus, Eurodis – Rare Disease Europe, Farmindustria.

From the debate between the institutions and other invited parties, two different documents have emerged: the II Booklet OSSFOR which reported on the regulation of the EAPs, and the Position Paper in which we report the proposals for solutions to improve the implementaion of the legislation.
With this document, OSSFOR aims to identify possible margins for improvement in implementing the legislation, with the ambition and the desire to indicate the possibility of solutions to overcome the critical issues related to it.
The various proposals of solutions identified refer, in some cases, to the long term and therefore to the prevision of legislative reforms of the various regulations, others of medium and short-term and therefore practical solutions that do not require the necessary intervention of the legislator, with the ultimate goal of facilitating the access of patients to these programs.

SOLUTIONS PROPOSED

What emerged from the study of the law on EAPs is that Italy, more than other European countries, pays special attention to the needs of early access for patients to drugs not yet authorized. This particular interest is demonstrated by the presence, in the Italian legal framework, of several rules that allow access to early treatment. In this specific case, the presence of a varied regulatory framework assumes undoubtedly a positive character, as it allows the patient to locate the procedure that more than others suits needs, in certain cases by invoking the help of the institutions and in others the manufacturers.
In the debate between the stakeholders, two main critical issues have been highlighted, connected in different ways to all the norms taken into consideration. In particular, reference is made to the need for an early dialogue between the parties called to intervene in the procedures described and governed by the rules and the greater sharing of information that, if implemented through generally shared systems, could lead to a reduction in the time required for the procedure. and, consequently, allow the patient to obtain the therapies in a short time.
Realizing the difficulty to initiate legislative reforms, the solutions proposed by OSSFOR, besides describing the future possibility of regulatory reform, also refer to the possibility of accelerated and simplified application. In this regard, various proposals have been divided according to the type of intervention proposed.

For implementation purposes (short-term solutions):

Law 648/96 -> Communication between parties involved in proceedings.

To facilitate the exchange of information between the partners involved in the delivery process of the drug, a way to allow dialogue of AIFA and the manufacturing companies should be found, not aimed at the insertion of a drug on the 648 list, but for the verification of the existing conditions for the dispensing of same drug

Law 326/03 -> Establishment of a register of authorizations to access the AIFA Fund.
Insert on the AIFA website a list of medications provided through the fund and related diseases, as is provided for DM 8 May 2003 and for the L. 648/96

-> Restore the direct reimbursement to businesses.

To reduce access times for patients, a situation of direct billing companies to AIFA should be restored, thus avoiding to go to the regions or to the local health authorities and therefore without increasing (albeit temporarily) on the same budget.

On a procedural level (medium term solutions):

Law 648/96 -> Setting up a registry to monitor the data.
To enable monitoring of the economic and clinical data of the drugs, an ad hoc register for the monitoring of drug data should be established, or making use of already existing registers, resulting in an identification code for the drugs used under law n .648/96.
To acquire a set of data already available to the manufacturers, provide for the involvement of the same companies by request, even in the verification phase, of the data already in their possession.

Law 326/03 -> Disemination of the procedure adopted for the authorization.
To reduce access times for patients it could be determined and diseminated (by publication) the procedure followed by AIFA for the authorization and by external parties involved foreseeing the release of the drug.

Law 648/96, Law 326/03 -> Resolution of critical issues related to the import of a product.
The solutions identified to avoid importing criticality could be:

- approval to start an EAP program must contain the consequential authorization for the drug entrance of our country;
- indicate the different behavior to be followed for the individual situations, e.g. unauthorized in any country, authorized EU country, authorized in a non-EU country;
- draw up guidelines on issues related to access of the drug on the Italian territory, for example. packaging criteria, not force - whenever possible - the repackaging.

In relation to this point, AIFA is currently engaged in the determination of a series of useful information to cope with different situations indicated above.

On a procedural level (long term solutions):

Law 648/96 -> Idea of legislative reform of the Institute
In view of a legislative reform of the institute, in addition to the elements already contained in the law, the new regulatory provision could contain:

- Involvement of companies when requesting inclusion on the list (as envisaged in the French ATU);
- preparation of a reference fund updated annually in view of the implementation of this solution, it is necessary to consider the impact on the 648 fund of off-label drugs for consolidated use, for this reason it would be appropriate to prepare a regulatory source exclusively dedicated to use of off- label and a fund dedicated to it;
- discipline for products that are denied reimbursement.

Law 648/96 -> Reduce the uncertainty related to time of negotiation

One of the elements that is relevant in the application of this legislation is the time factor, in fact, during the price / reimbursement negotiation procedure, the institutions support the costs related to the drug. In order to give an indication of the necessary waiting time, stopping rules could be used, established from time to time depending on the state of progress of the regulatory procedure concerning the medicine.

In order to give concrete application to the solutions hitherto envisaged, OSSFOR suggests further study, perhaps through bilateral meetings, of some specific themes emerged from the preparatory work of this Position Paper.

In this regard, until now the topics on which to open the debate again are:

- the sharing of information between the subjects involved in the proceeding, in the case between AIFA and the companies producing the drug included in the 648 list;
- identify a method for collecting data on clinical and economic monitoring, avoiding excessive burdening of AIFA systems and investing new economic resources when the existing registers could be implemented.

THE NEW D. M. 7 SETTEMBRE 2017 ("COMPASSIONATE USE")

The discussion conducted by OSSFOR on the law also concerned the Ministerial Decree of 8 May 2003, "Therapeutic use of a medicine subjected to clinical trials". This Decree was repealed, without prejudice to the ongoing programs for which it continues to be applied, by the ministerial decree of 7 September 2017. In order to complete this Position Paper it was considered appropriate to include the discussion regarding the ministerial decree of the 7 September 2017, with which the Minister of Health has implemented the provisions of art. 158, paragraph 10 of Legislative Decree n. 219 of 2006, on "Implementation of Directive 2011/83 / EC (and subsequent amending directives) relating to a Community code concerning medicinal products for human use, as well as Directive 2003/94 / EC" which provides that by decree of the Minister of Health, are established, also taking into account the Guidelines issued by EMA, the criteria and methods for the use of medicinal products without AIC in Italy and the compassionate use of medicines not yet registered. The new decree, repealing with effect from the date of entry into force, the Ministerial Decree of 8 May 2003 which continues to be applied to the procedures in progress at the date of entry into force of the new decree.
With the new Ministerial Decree, the Ministry of Health, has solved a series of critical issues related to the Ministerial Decree of 8 May 2003 found during the work conducted by OSSFOR on the topic. Much of this criticality has been resolved with the new D.M., while others remain open questions.

- Establish a specific provision containing rules on compassionate use.

This provision is contained in art.158, paragraph 10 of Legislative Decree 219/06, according to which, taking into account the guidelines of the EMA for the compassionate use of medicines, the criteria and modalities are established, among others, to regulate the compassionate use of medicines not yet registered.
According to OSSFOR, in fact, the requirements set by the D.M. May 8, 2003, "Therapeutic use of an investigational medicinal product" did not always respond to the needs of rare diseases or to situations of last hope of care where the scientific evidence is very low, often based on case studies. This criticality was resolved by paragraph 3 of the art. 2 of the D.M. 7 September 2017, which provides that for rare diseases or rare tumors, at least Phase I clinical trials, which have already documented the activity and safety of the medicinal product, should be available at a specified dose and schedule of administration, in indications also different from that for which compassionate use is required. The possibility of obtaining a clinical benefit from the medicinal product must be reasonably founded in basis of the mechanism of action and the pharmacodynamic effects of the medicinal product.

- Communication between the subjects involved in the procedure.

Many of the delays and complications found during the drug delivery process, according to OSSFOR, could be solved through the prior communication by the manufacturers of the launch of the extended access programs to AIFA, which included them in the list of drugs disbursed as a Decree of May 8, thus avoiding operational complexity with the USMAF.
This problem was resolved by Article 5, which requires that pharmaceutical companies wishing to activate compassionate use programs in Italy are required to inform the AIFA in advance of the activation date and closure of the program, indicating the medicine they intend to provide freely and declaring the period of presumable availability for the free supply of the medicine. In addition, the closing communication of the compassionate use program must be forwarded to AIFA at least thirty days before the closing date.

- Critical issues related to the importation of a product.

From the study carried out by OSSFOR, there were delays related to the importation of products

subjected to experimentation from abroad, as there was no list of the technical requirements that products must have to access the territory of our country, in the same way not all the extended access programs were communicated to AIFA, which consequently did not include them in the list present on the site, consulted by the USMAF to authorize access to the medicines.
In this regard, paragraph 6 of the art. 4 of the D.M. September 7, 2017 provides that the USMAF SASN territorially competent allows the entry of the medicine from abroad, upon presentation of a special application accompanied by a copy of the favourable opinion given by the Ethics Committee, according to the procedures set by the Decree of the Minister of Health 11 February 1997, establishing rules on "How to import medicinal products registered abroad".

- Reduce uncertainty about negotiation times.

One of the elements that is relevant in the application of this regulation is the time factor, in fact, during the price / reimbursement negotiation procedure, the manufacturing companies bear the costs related to the drug. In order to provide an indication of the necessary waiting time, according to OSSFOR, stopping rules may be established and established, identified from time to time depending on the state of progress of the regulatory procedure concerning the medicine and the creation of a preferential channel for the negotiation of drugs provided by the company in accordance with the DM May 8th.

This criticality appears to be resolved, in part, by paragraph 6 of the art. 4 of the new D.M., reported in the previous point.
However, it does not seem to be specified what happens after the end of the compassionate use program, or rather what happens when the term indicated by the pharmaceutical companies expires. In this regard, at the end of this period, how is the continuity of therapy ensured for patients treated? And again, in the event that the latter continues to be insured, who is the subject on which the burden of costs weighs? These questions remain an open question, as they are not specified in the new Ministerial Decree of 7 September 2017.

Consorzio per la Ricerca Economica Applicata in Sanità

C.R.E.A. Health (Consortium for Economic Research Applied in Healthcare) is a non-profit-making consortium promoted by the University of Rome Tor Vergata and FIMMG (Italian Federation of General Practitioners). The Consortium was born in July 2013, over twenty years of experience and the expertise of a multidisciplinary team of coordinated researchers, always at the University of Tor Vergata, by Prof. Federico Spandonaro, currently President of the Consortium. Team that over the years has become a point of excellence for economic and organizational research in the health field.

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

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

Osservatorio Malattie Rare – O.Ma.R.
www.ossevatoriomalattierare.it
Contact: direttore@ossevatoriomalattierare.it

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