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Rare Diseases Italy


# MonitoRare

## 4rd Report on the condition of people living with Rare Disease in Italy

year
2018

# index

# executive summary

Again this year, the "MonitoRare" Report provides much food for thought, open to further consideration. In these first few pages, we will try to effectively summarize the Report's fourth edition, with the sole aim of considering some key elements that, more than others, play a major role for the future of the care provided to rare disease patients (RDP) and their families at the international, national and local level.

First of all, it is worth reminding that 2017 was a year characterized by the **adaptation** by Regions/Public Administrations (PAs) **to the new list of rare diseases provided for in art. 52 and Annex 7 of Prime Minister Decree** "*Definition and update of the essential levels of care, provided for in article 1, paragraph 7, of Legislative Decree of 30 December 1992, no. 502*", **of the regional networks for rare diseases** through the identification of the relevant centres **and of the Regional Registries for Rare Diseases** (RRRD). All Regions/PAs succeeded in the task, even though some them did after the deadline of 180 days of the entry into force of the Decree, published in the Official Journal of March, 18th 2017.

Another important area of activity for Regions/PAs during the last year was **the start of the implementation of expanded newborn screening** for hereditary metabolic disorders, as provided for by the Decree of the Ministry of Health of 13 October 2016 "*Provisions for the implementation of newborn screening for the early diagnosis of hereditary metabolic disorders*", which is being carried out at different paces in different areas.

The third important area, where Regions were engaged in the more general scope of intervention regarding disabled persons, was the definition of the **intervention programmes of the Fund for the care to seriously disabled persons without family support** (Law no. 112/2016): to this day, such interventions – made possible by the funds allocated (90 million € for 2016 and 38 million € for 2017) – have been carried out only in 4 Regions.

Apart from these very positive and long-awaited measures, that were tenaciously pursued by rare disease patients and their representatives/associations, some negative "systemic" issues persist; first of all:

- **non-establishment of the National Committee provided for by the National Plan for Rare Diseases (NPRD) 2013-2016;**
- **no evaluation of the NPRD 2013-2016;**
- **no launch of the new planning of the sector.**

The other more specific issues – examined more into details in the full Report – could be summarized, as we did last year, by saying that "**strengths are consolidated while weaknesses persist".**

Some of the strengths of the Italian rare diseases systems that are confirmed by the fourth edition of MinitoRare are:

- **accessibility of drugs** *(Annex 1)*
  - **the overall number of orphan medicinal products available in Italy at the end of 2017 was 94**. The **new approvals** by AIFA – Italian Medicines Agency- during the last year were **14**, in line with the average of the period 2014-2016 (15 approvals);
  - the **use of orphan medicinal products from 2013 to 2017 increased by 69.3% in absolute terms and by 66.6% in relative terms** in the total use of drugs;
  - **the expenditure for orphan medicinal products grew from 917 million € in 2013 to 1,599 million € in 2016 (+74.4%):** over the same period, **the incidence of expenditure for orphan medicinal products in the total pharmaceutical expenditure grew from 4.7% to 7.2% (+54%)**;
  - **the number of orphan medicinal products for rare diseases included in the list of Law n. 648/1996 grew from 13 in 2012 to 28 in 2017**; *The Italian Law 648/96 allows, on the costs of the National Health Service, the use of three types of medical products: innovative drugs for which the sale is authorized abroad, but not in Italy; drugs which have not yet received an authorization, but have undergone clinical trials; and drugs to be used for a therapeutic indication different from the one which had been authorized (off-label).*
  - as many as **82 rare disease patients** (out of 126 applications – 65.1%) **benefited from the AIFA Fund** (provided for by Law 326/2003, art. 48) for a total amount of **expenditure of more than 14 million €** (7.4 million € in 2016; 1.1 million € in 2015); *Article 48 of Law 326/2003 requires all drugs companies operating in Italy to pay 5% of their promotional expenses to an independent research fund (Fondo AIFA 5%). This fund is designed to promote orphan diseases research and to make available to rare diseases' patients medicines awaiting market entry. Therefore, according to the law, half of the fund should be devoted to providing access to medicines for rare diseases before market authorization, and the other half should be devoted to promote independent research and related activities.*

- **quality and coverage of monitoring systems**
  - **the coverage of the Regional Registries for Rare Diseases has increased**: the **prevalence in the population** of persons entered in RRRDs grew from 0.30% of MonitoRare 2015 to **0.53%**. According to RRRDs data, the overall **number of persons affected by a rare disease** in our country may exceed 770,000 units, with a prevalence of 1.27 in the population (this is probably an underestimate as some RRRDs do not yet cover the population completely);
  - only **1 rare disease patient in 5 is younger than 18**; women show a slightly higher prevalence as compared to men (52% *vs*. 48%)
  - **in Italy**, roughly **41,000 new cases were entered in RRRDs last year**

- **research** *(Annex 3)*
  - **the ratio of approved clinical trials on rare diseases slightly increased in the total number of clinical trials**: from **20.0%** in **2013** to **25.5%** in **2017**, even in a context of overall decrease of the number of clinical trials carried out during last year (144 in 2017 *vs.* 164 in 2016);
  - the ratio of **biological/bio-technological active substances** has grown and **accounts for 37.5% of the total number of clinical trials on rare diseases**, while chemical active substances account for 51.4%;

[1] Source: AIFA list (including both orphan and "orphan-like" medicinal products, in addition to the drugs for the treatment of the rare diseases listed in the Orphanet Register).

- the presence of **Italian research teams in projects concerning rare diseases within the Orphanet platform** remains high: **19.9% in 2017**, slightly decreasing as compared to 2016, but higher than 18.3% of 2014;
- **268 current research projects on rare diseases carried out by IRCSSs – Scientific Institute for Research and Care -in 2017 (8.4%** of the total, slightly decreasing as compared to the previous year) **for a total amount of more than 11.5 million €** (9.1% of the total);
- **7.6 million € (18.2%** of the total): the resources of **dedicated healthcare research** invested on projects concerning rare diseases (firmly growing as compared to the previous year);

■ **clinical laboratories**
- **constant growth over the last five years of the number of diseases tested in the clinical laboratories** listed in the Orphanet database, that **increased by more than 35%** (from 1,107 to 1,503);

■ **quality of centres of expertise**
- **Italy ranks first for the number of healthcare providers (HCPs) members of the *European Reference Networks* (ERNs):** 189 out of 942 in total (20.1%); Italian HCPs are present in all but one ERNs (only France, Netherlands and Belgium are present in all the 24 ERNs). On average there are 6 Italian HCPs for in each ERN

■ **active involvement of patients**
- **The representatives of Italian patients involved in the 24** formally constituted ***European Patient Advocacy Groups* (ePAGs) are 36** out of **218 (16.5%**; they were 25 in 2017**); 15** out of 24 **(62.6%) ePAGs have at least one Italian representative** (*Annex 2*);
- **3 representatives of rare disease patients are members of the "Coordination Centre for newborn screening"** provided for by art. 3 of Law no. 167 of 19 August 2016 "*Provisions on compulsory neonatal diagnostic tests for the prevention and the treatment of hereditary metabolic disorders*";
- **one representative of rare disease patients has been appointed as a member of the National Coordination Centre for Local Ethics Committees** provided for by Law no.3 of 11 January 2018 "*Delegation to the Government on the matter of clinical trials of medicinal products and provisions for the reorganization of health professions and for the management of the healthcare system by the Ministry of Health*".

The other side of the coin is represented by the weaknesses that persist, such as:

■ **Territorial heterogeneity in the access to health and social services,** for example:
- inequalities in the geographical distribution of the Italian hospitals taking part in ERNs: 66.7% (n=44) of hospitals taking part in at least one ERN are located in northern regions; 19.7% (n=13) in the centre of Italy and just 13.6% (n=9) in southern Italy;
- different degrees of regulation of the administration of pharmacological and non-pharmacological treatments at school, specifically regulated in 11 Regions/Public Administrations;
- lack of relief programmes at competent non-hospital centres (with stay) for rare disease patients; such programmes are in planning or implementation phase just in 9 Regions/Public Administrations;

- **failure to implement the administrative tools that are needed to recognize and ensure the adequate remuneration for remote consultancies provided by hospitals/centres of expertise;**

- **failure to implement managing and administrative solutions aimed at assessing the feasibility of the types of remuneration taking account of the complexity of the management of rare disease patients in the hospital and territorial settings;**

- **failure to involve the representatives of associations of rare disease patients in the Coordination and Monitoring Body for the development of ERNs (Ministerial Decree of 27 July 2015, as provided for by art. 13, paragraph 2, of Legislative Decree no. 38 of 4 March 2014).**

# The Italian situation in figures

# The Italian situation in figures

The following tables and in depth information on OMPs and ERNs are meant to provide a clear update on these two topics

## Annex I – Orphan Medicinal products

*Information objective*

**Number of orphan medicinal products approved in the European Union and available in Italy over the past five years (figure on 31 Dec. of each year)**

| Year | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|
| Total number of orphan drugs available in Italy (on 31 Dec.) | 41 | 52 | 66 | 71 | 92[2] |
| Number of orphan drugs approved by EMA entered in the EU Register | 59 | 72 | 87 | 91 | 99 |

*Information objective*

**Expenditure and consumption of orphan medicinal products in Italy over the past 5 years and comparison with the total pharmaceutical expenditure and consumption[3]**

| Year | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|
| Consumption of orphan medicinal products (in DDD) (Mln) | 7.5 | 8.5 | 10.3 | 11.4 | 12.7 |
| % of total consumption | | | | 0,04% | 0,05% |
| Total amount of expenditure for orphan medicinal products (Mln €) | 917 | 1.060 | 1.212 | 1.393 | 1.599 |
| % of total expenditure | 4,67% | 5,31% | 5,49% | 6,12% | 7,19% |

| Source | Reference period | Type of information | Area of the reference NPRD |
|---|---|---|---|
| AIFA | 2013-2017 | Output | 10 |

[2] The figure grows to 94 if we consider the total amount of medicinal products present in the AIFA list, including both orphan and "orphan-like" medicinal products, in addition to the drugs for the treatment of rare diseases listed in the Orphanet Register.

[3] The data on expenditure and consumption have been processed since 2013 according to the new classification approved by AIFA Board of Directors (Decision no. 10 of 27 February 2014), including orphan medicinal products belonging to the class of drugs non-refunded by the NHS; such results can be compared to those coming from previous years. Data include the expenditure and consumption for reimbursed care provided by local pharmacies (both private and public) and for the purchases of medicinal products by public healthcare facilities.

*Remarks*

Owing to the complex path going from the designation to the approval, there are still few orphan medicinal products that have obtained the marketing authorization (MA) after the orphan designation: less than 10%[4]. According to the recent analysis carried out by the Observatory for Orphan Medicinal Products (OSSFOR) "*at the European level, the time from the orphan designation and the request for the marketing authorization through the EMA centralized procedure is increasing: from 34 months (median: 31) for EMA approved drugs in 2003 and 2004, to 74 months (median: 77) in the period 2015-2016. Such an increase is associated to a reduction in the duration of the EMA authorization process, showing that the first phenomenon is the effect of an increasingly early designation*"[5]. The same source indicates that, thanks to the regulatory changes implemented in the past few years to improve the access to drugs *"at the national level (AIFA), in recent years a trend has been observed towards the reduction in the duration of the process: the period between the EMA authorization, the pricing and the reimbursement decreased from 29 months (median: 26) in the 2011-2013 period, to 13 months (median: 12) in the period 2014-2016"*.

Recently, in Italy the total number of orphan medicinal products available has increased: at the end of 2017 they were 94[6] (including those belonging to Cnn and C classes, with a percentage of the total number of EMA approved orphan medicinal products in line with the data from the previous years). We should also not forget that some other drugs are accessible on the territory through other supply channels (Law 648/1996 and art. 8 of Law 326/2003) and are made available to patients by the Italian Medicines Agency. Moreover, there are other orphan medicinal products with an expired 10-year market exclusivity – granted by EMA – that were therefore removed from the European Registry.

Over the last year, 14 new approvals were granted by AIFA, confirming the trend of the previous period (on average, 15 per year in the period 2014-2016). The increase in the number of orphan medicinal products goes hand in hand with an increase both in the consumption of orphan medicinal products (in terms of defined daily dose – DDD[7]), growing from 7.5 million in 2013 to 12.7 million in 2017 (+69%), and in the expenditure for orphan drugs, growing from 917 million € in 2013 to 1,599 million € in 2017 (+74%).

In the five-year period 2013-2017, the incidence of the consumption of orphan medicinal products in the total consumption of drugs grew from 0.3% to 0.5%, while the incidence of the expenditure for orphan medicinal products grew from 4.7% to 7.2%, with a more marked growth in 2017 as compared to the previous year.

*Information objective*

**Total number of medicinal products present in the list provided for by Law 648/1996 for rare diseases over the past 5 years (figure on 31 Dec. of each year) and number of new entries for each of the past 5 years.**

| Year | Number of medicinal products present in the list of Law 648/1996 for rare diseases (figure on 31 Dec. of each year) | Number of new entries per year |
|---|---|---|
| 2013 | 21 | 11 |
| 2014 | 22 | 5 |
| 2015 | 27 | 5[8] |
| 2016 | 27 | 1 |
| 2017 | 28 | 2 |

[4] Source: European Medicines Agency/Rare disease (orphan) designations

[5] Observatory for Orphan Medicinal Products, "OSSFOR 1st Annual Report – Impact and Governance of rare diseases and orphan medicinal products", November 2017

[6] According to the criteria laid down by AIFA Board of Directors, the figure includes also orphan-like products.

[7] The *defined daily dose* (DDD) is the standard unit for pharmaceutical prescription, defined by the World Health Organization as the *"assumed average maintenance dose per day for a drug used for its main indication in adults"* (http://www.whocc.no/ddd/definition_and_general_considera/)

[8] This figure includes Cladribina, entered in the 648/96 list of drugs with well-established use for the treatment of Langerhans cell histiocytosis

*Information objective*

**Applications for the approval of the off-label use of drugs for rare diseases submitted over the past 5 years and status of requests on 31 Dec. 2017**

| Year | Number of drugs for which the approval for the off-label use for rare diseases was requested | Status of applications by type of outcome | |
|---|---|---|---|
| | | N | |
| 2013 | 4 | 4 | Accepted |
| | | - | Under assessment |
| | | - | Rejected |
| 2014 | 5 | 5 | Accepted |
| | | - | Under assessment |
| | | - | Rejected |
| 2015 | 16 | 5 | Accepted[9] |
| | | 2 | Under assessment |
| | | 9 | Rejected |
| 2016 | 15 | 1 | Accepted |
| | | 4 | Under assessment |
| | | 10 | Rejected |
| 2017 | 13 | 5 | Accepted |
| | | 0 | Under assessment |
| | | 8 | Rejected |

[9] See previous note

## Annex 2 – European Reference Networks and ePAGs

| ID | ERN acronym | ERN description | Total no. of HCPs | No. of HCPs in Italy | Total no. of ePAGs | No. of ePAGs in Italy |
|---|---|---|---|---|---|---|
| 1 | ERN BOND | European Reference Network for bone diseases | 38 | 7 | 3 | 0 |
| 2 | ERN EURACAN | European Reference Network for adult cancers (solid cancers) | 67 | 17 | 8 | 0 |
| 3 | ERN ReCONNET | European Reference Network for connective tissue and musculoskeletal diseases | 27 | 8 | 7 | 1 |
| 4 | ERN CRANIO | European Reference Network for craniofacial anomalies and ear, nose and throat disorders | 28 | 6 | 3 | 0 |
| 5 | Endo-ERN | European Reference Network for endocrine conditions | 71 | 9 | 11 | 2 |
| 6 | ERN EYE | European Reference Network for eye diseases | 29 | 6 | 7 | 1 |
| 7 | ERNICA | European Reference Network for congenital and hereditary diseases | 20 | 1 | 10 | 0 |
| 8 | ERN PaedCan | European Reference Network for paediatric cancers | 57 | 10 | 5 | 0 |
| 9 | ERN Euro BloodNet | European Reference Network for rare haematological diseases | 65 | 21 | 6 | 1 |
| 10 | ERN RARE-LIVER | European Reference Network for liver diseases | 28 | 3 | 21 | 0 |
| 11 | MetabERN | European Reference Network for hereditary metabolic diseases | 69 | 11 | 5 | 4 |
| 12 | ERN RITA | European Reference Network for immunodeficiency, autoinflammatory and autoimmune diseases | 24 | 5 | 8 | 2 |
| 13 | ERN ITHACA | European Reference Network for congenital malformations and rare intellectual disability | 33 | 8 | 16 | 2 |
| 14 | VASCERN | European Reference Network for multisystemic vascular diseases | 17 | 8 | 13 | 4 |
| 15 | ERN-RND | European Reference Network for neurological diseases | 32 | 4 | 8 | 2 |
| 16 | ERN EURO-NMD | European Reference Network for neuromuscular diseases | 61 | 15 | 6 | 1 |
| 17 | ERKNet | European Reference Network for kidney diseases | 38 | 11 | 11 | 0 |
| 18 | ERN Skin | European Reference Network for skin diseases | 56 | 5 | 19 | 4 |
| 19 | ERN eUROGEN | European Reference Network for urogenital diseases and conditions | 29 | 4 | 3 | 2 |
| 20 | ERN LUNG | European Reference Network for respiratory diseases | 60 | 15 | 19 | 4 |
| 21 | ERN GENTURIS | European Reference Network for genetic tumour risk syndromes | 23 | 0 | 6 | 2 |
| 22 | ERN EpiCARE | European Reference Network for epilepsy | 28 | 5 | 10 | 2 |
| 23 | ERN TRANSPLANT-CHILD | European Reference Network for paediatric transplantation | 17 | 4 | 5 | 1 |
| 24 | ERN GUARD HEART | European Reference Network for cardiac diseases | 25 | 6 | 8 | 1 |
| **TOTAL** | | | **942** | **189** | **218** | **34**[10] |

European Reference Networks

[10] 2 persons are ePAG representatives in two different ERNs

## Annex 3– Clinical trials

### Clinical trials – Total number of clinical trials authorized in the past 5 years in Italy and Europe

| Year | Italy | of which, on rare diseases: | Europe |
|---|---|---|---|
| 2013 | 583 | 117 (20,0%) | 3.383 |
| 2014 | 592 | 139 (23,5%) | 3.249 |
| 2015 | 681 | 167 (24,8%) | n.a. |
| 2016 | 650 | 160 (24,6%) | n.a. |
| 2017 | 564 | 144 (25,5%) | n.a. |

### Clinical trials – Total number of clinical trials on rare diseases authorized by type of promoter and extension for the years 2014 – 2015 – 2016

| Type of promoter | National | | | | | | International | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2014 | | 2015 | | 2016 | | 2014 | | 2015 | | 2016 | |
| | SC | % | SC | % | SC | % | SC | % | SC | % | SC | % |
| Profit | 5 | 20,0 | 1 | 4,8 | 1 | 5,6 | 99 | 86,8 | 138 | 94,5 | 137 | 93,8 |
| No profit | 20 | 80,0 | 20 | 95,2 | 17 | 94,4 | 15 | 13,2 | 8 | 5,5 | 9 | 6,2 |
| Total | 25 | 18,0 | 21 | 12,6 | 18 | 11,0 | 114 | 82,0 | 146 | 87,4 | 146 | 89,0 |

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