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Rare disease policies to improve care for patients in Europe☆

Charlotte Rodwell *, Ségolène Aymé

INSERM, US14—Orphanet, France

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ABSTRACT

Rare diseases are those with a particularly low prevalence; in Europe, diseases are considered to be rare when they affect not more than 5 in 10 000 persons in the European Union. The specificities of rare diseases make the area a veritable public health challenge: the limited number of patients and scarcity of knowledge and expertise single rare diseases out as a distinctive domain of high European added-value. The Orphan Medicinal Product Regulation of 1999 was the first European legislative text concerning rare diseases, followed by many initiatives, including recommendations by the Council of Ministers of the European Union in 2009. These initiatives contributed to the development of rare diseases policies at European and national level aimed at improving care for patients with rare diseases. A review of the political framework at European level and in European countries is provided to demonstrate how legislation has created a dynamic that is progressively improving care for patients with rare diseases. This article is part of a Special Issue entitled: "Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease)".

1. Introduction

Rare diseases are those with a particularly low prevalence. The threshold to define rarity differs across countries and regions; the European Union considers diseases to be rare when they affect not more than 5 in 10 000 persons in the European Union. This definition first appeared in the 1999 Regulation (EC) 141/2000 on Orphan Medicinal Products [1], and it is estimated that around 7000 rare diseases exist [2]. The Orphan Medicinal Product Regulation of 1999 was the first European legislative text concerning rare diseases and represented the start of a commitment at European level to the development of rare diseases policies at European level aimed at improving care of patients with rare diseases. The specificities of rare diseases make the area a veritable public health challenge: the limited number of patients and scarcity of relevant knowledge and expertise single rare diseases out as a distinctive domain of high European added-value [3]. European cooperation can help ensure that scarce knowledge is shared and resources are combined as efficiently as possible, in order to tackle rare diseases across the European Union as a whole. This paper will provide a review of the political framework at European level and in European countries to demonstrate how legislation has created a dynamic that is progressively improving care for patients with a rare disease in areas as diverse as organisation of healthcare, diagnostics, research, therapies, information services and patient support.

2. Materials and methods

A review of the state of the art of rare disease policy and activities at National, European and International levels was conducted, based on the work carried out by the European Union Committee of Experts (EUCERD) Joint Action Scientific Secretariat in order to produce the annual "Report on the State of the Art of Rare Diseases Activities in Europe" [4], in particular the first volume of the 2014 edition of this report which provides an overview of the state of play and initiatives in the field. The main legislative texts in the field of rare diseases at national, European and International level were also examined. The survey also took into consideration the information published by the newsletter of the rare disease community, OrphaNews [5], in addition to the sources of the "Report on the State of the Art of Rare Diseases Activities in Europe" as cited in its bibliography.

The impact of European and national rare disease related policies on the various sectors of activities at play within the field of rare diseases is presented in the results.

3. Results

3.1. Political framework

Political concepts and initiatives in Europe concerning rare diseases progressively emerged at the end of the 20th century at both European Union (EU) and Member State (MS) level, paving the way for the

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* Corresponding author at: INSERM US 14—Orphanet, Rare Diseases Platform, 96 rue Didot, 75014 Paris, France. Tel.: +33 1 56 53 81 37.
E-mail address: charlotte.rodwell@inserm.fr (C. Rodwell).

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adoption of a series of legislative texts which defined European policy in the field. Sweden, for example, established the first centres of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999; Denmark established an information centre in 1990 and centres of expertise for rare diseases in 2001; in France, the rare disease and orphan drug database Orphanet was established in 1997 with the support of the French Ministry of Health and the INSERM (French National Institute for Health and Medical Research), followed by a national plan for rare diseases in 2004 which was the first of its kind in the world. Around the same time, a number of other countries in Europe (Bulgaria, Greece, Portugal and Spain) were elaborating a national plan or strategy for rare diseases, whilst the EU policy in the field was defined through the European Commission (EC) Communication on Rare Diseases (2008) [3], and the Council Recommendation on an action in the field of rare diseases (2009) [6], building on the previously mentioned 1999 Regulation on Orphan Medicinal Products. Today, policy at national level is generating momentum in the wake of EU policy in response to the Council Recommendation's call for countries to adopt a national plan or strategy aimed at guiding and structuring actions in the field of rare diseases within the framework of their health and social systems. Twenty of the twenty-eight countries in the EU have adopted such a plan or strategy to date and the others are in the process of adopting their plan or strategy (Fig. 1).

3.1.1. European level

Four key policy documents have established the political framework for action in the field of rare diseases and orphan medicinal products at European level. Firstly in 1999, the Orphan Medicinal Product Regulation N° 141/2000 [1] of the European Parliament and the Council on orphan medicinal products established the criteria for orphan designation in the EU and described the proposed incentives to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. This Regulation also established the European definition of a rare disease as a disease with a prevalence of not more than 5 per 10 000 persons in the European Union. Fifteen years after its adoption, the Regulation can be seen as a success (see 3.5) with over 80 orphan medicinal products having received market authorisation to date.

This Regulation provided the basis for the development of an overall EU strategy to support countries in the diagnosis, treatment and care of their citizens with a rare disease. In 2008, the EC published a report on Rare Diseases [3], entitled *Rare Diseases: Europe's Challenge,* which recognised the potential for maximising the scope for cooperation and mutual support in this singular area across Europe as a whole. It highlighted the need to improve the recognition and visibility of rare diseases, to support policies on rare diseases in MS for a coherent overall strategy, and to develop cooperation, coordination and regulation for rare diseases at EU level. Based on this report and the wide-ranging objectives it set for the European community, the European Council of health ministers adopted in 2009 a Recommendation on an action in the field of rare diseases [6]. Engaging the responsibility of European countries, the Recommendation encourages the elaboration and adoption of national plans and strategies for rare diseases by the end of 2013. Countries were encouraged to consider in these plans/strategies aspects such as the improvement of the recognition and visibility of rare diseases, encouragement of research into rare diseases, the development of links between experts and centres of expertise in different countries to identify and pool expertise at European level, the empowerment of patient organisations, and the development of sustainability in the field of information, research and healthcare infrastructures.

To help the EC in the implementation of the objectives of the Commission Communication and Council Recommendation, the European Committee of Experts on Rare Diseases [7] (EUCERD) was established in 2009. The EUCERD followed in the footsteps of the EC's Rare Diseases Task Force which was the first committee of its type at European level, meeting from 2004 to 2009. The EUCERD was a multi-stakeholder forum that succeeded in adopting, during its 3 year mandate, 5 sets of recommendations aimed at guiding the EU and Member States in the

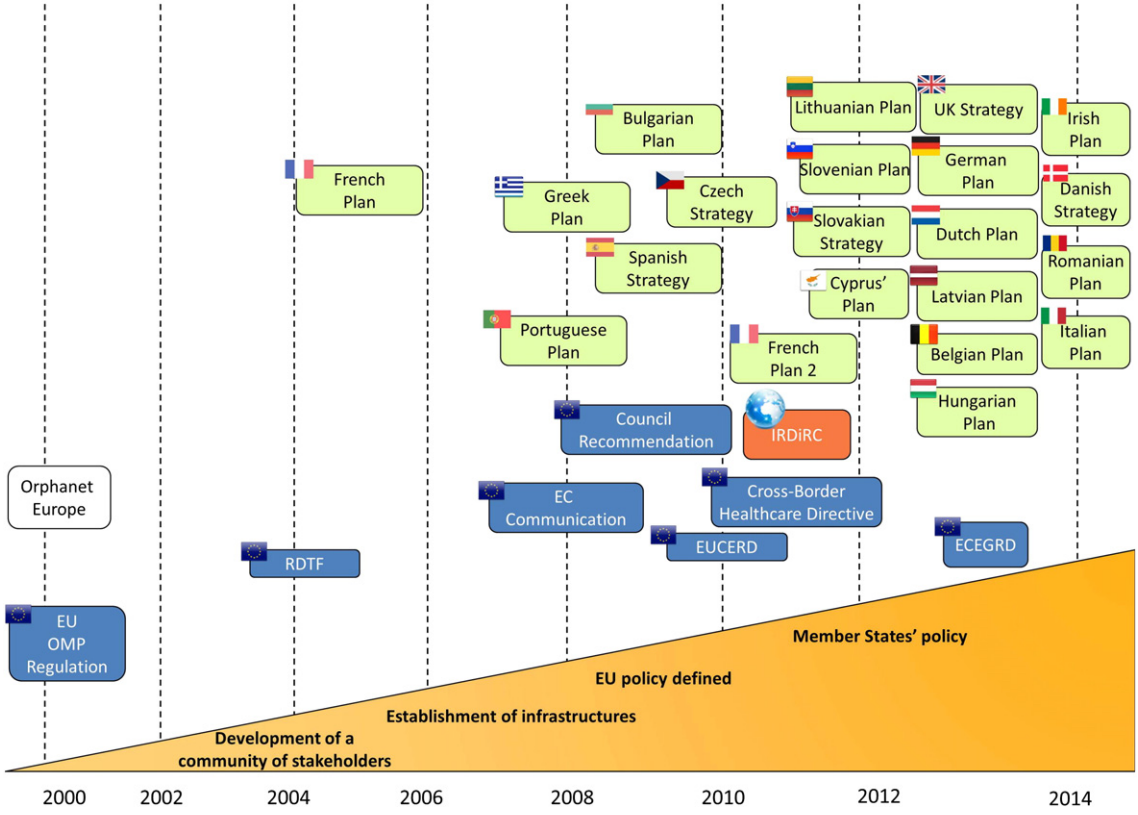

Fig. 1. Evolution of rare disease policy in Europe (December 2014) [4].

implementation of rare disease policies. At the end of 2013, the Committee was replaced by the EC Expert Group on Rare Diseases (EGRD) [8] which continues to aid the EC in shaping their rare disease policies.

European financing was also provided to a number of projects to support the EU policy in the field in the framework of the Second Programme of Community Action in the Field of Public Health [9].

The Commission published in 2014 a report [10] that considered the extent to which the proposed measures of the Commission Communication and Council Recommendation are working effectively to make improvements in the field. The report takes stock of the successes to date, and outlines the EU's intention to maintain a coordinative role in the development of the EU policy on rare diseases and to support Member States in their national activities in this field.

Rare diseases were also specifically addressed in Directive 2011/24/EU on the application of patients' rights in the cross-border healthcare [11], approved in 2011. This Directive seeks to facilitate access to health care for EU citizens and encourage cooperation between EU MS in the field of health, of particular interest in the field of rare diseases where patients and expertise are rare and scattered across the EU. In particular, the Directive encourages the establishment of European Reference Networks in the field of rare diseases to pool expertise and improve care for patients.

3.1.2. National level

At national level in Europe, the state of play as regards the development of national rare disease policies, plans and strategies differs greatly from country to country: whereas France is reaching the end of a second National Plan for Rare Diseases, some countries are still in the process of bringing together stakeholders to determine where action is needed. The Council Recommendation [6] has served as a catalyst in the development of national plans and strategies for rare diseases in EU countries. Whereas only 5 countries had developed such a plan or strategy at the time of its adoption in 2009, by the end of 2013 (the date by which the Council Recommendation encouraged countries to adopt a plan) 16 countries had adopted a plan/strategy with the others in advanced stages of the elaboration of a plan/strategy. Four additional countries adopted a plan/strategy by the end of 2014, bringing the total to 20 out of the 28 European Union Member States (Table 1).

These plans/strategies vary in their scope and their financing which will ultimately influence the extent of their impact at national level. Some countries have still to define the elements outlined in their policies in specific work plans. The main issues of concern tackled by these policies are: the organisation of expert care for rare diseases within the existing healthcare system, the adequate coding of rare diseases within health information systems, the registration of patients with rare diseases at national level, and the provision of information on rare diseases through support to the European rare disease and orphan drug database, Orphanet [12].

It should be noted that the current economic context is having a negative impact on the development and implementation of these plans: many plans may have insufficient or no funding as a result, thus potentially limiting their impact.

3.1.3. Other world regions

Outside of the European region, a number of countries have developed political frameworks in the field of rare diseases. Mostly, these initiatives concern the regulation of orphan medicinal products. Policies for orphan medicinal products started as early as 1983 in the United States with the adoption of the Orphan Drug Act, then in Japan (1993) and in Australia (1997). Europe followed suit in 1999 by implementing a common EU policy on orphan medicinal products [1]. The European Council Recommendation on an action in the field of rare diseases [6] and the elaboration of national plans/strategies in European countries is inspiring other countries around the world to consider the necessity of a national policy for rare diseases and efforts are being made in a number of countries to explore possibilities in this area [4].

3.2. Centres of expertise and European Reference Networks

3.2.1. Centres of expertise for rare diseases

The identification, and creation, of centres of expertise for rare disease is a key element of the Council Recommendation and central to national rare disease plans/strategies. With around 7000 rare diseases identified to date, the majority unknown to healthcare professionals, rare disease patients suffer from not knowing where to consult. To overcome this, some EU countries have established centres specialised in some rare diseases/groups of rare diseases which have proven to be very efficient in improving the quality of care for rare disease patients. The networking of these centres could lead to the gathering of the scarce expertise concerning these diseases at European level, in order to ensure equal access to accurate information, appropriate and timely diagnosis and high quality care for rare disease patients.

Currently, the organisation of centres of expertise varies greatly from country to country in Europe: few countries currently have a designation process in place and the designation criteria vary from country to country, and sometimes even from region to region within a country (Table 2).

In order to provide guidance to countries wishing to elaborate similar processes within the scope of their national plans/strategies for rare diseases, the EUCERD established a set of Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States in 2011 [13].

These recommendations outline the mission and scope of such centres, the general quality criteria to be considered in a designation process, guidance concerning the evaluation procedures for centres of expertise, and the European dimension of these centres in terms of their future implication in the European Reference Networks (ERNs) to be created within the scope of the Directive on the application of patients' rights in cross-border healthcare. These ERNs are supposed to be networks, at European level, between national centres of expertise.

Many countries are currently using and/or adapting these recommendations to their national context, mostly within their national plans/strategies: this action will both provide better care for patients at national level, and also to prepare for the implementation of European Reference Networks. As a result, the designation criteria adopted should be relatively homogenous from country to country

Table 1
State of evolution of national plans/strategies in European Union Member States in December 2014 [4].

- National plans/strategies fully implemented: France, Spain
- National plans/strategies adopted: Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Portugal, Romania, Slovak Republic, Slovenia, the Netherlands, and United Kingdom.
- National plan/strategy submitted to national authorities: Austria, Croatia, Estonia, Finland, Malta, Poland, and Sweden.
- Drafting group/stakeholder meetings being held: Luxembourg

Table 2
State of the art of centres of expertise at national level in European Member States in December 2013 [4].

- Centres of expertise designated in the context of a national rare disease plan/strategy: France
- Centres of expertise designated outside of a national RD plan/strategy: Denmark, Italy (regional), Spain, Sweden, and United Kingdom.
- Countries with plans to designate centres of expertise within a national rare disease plan/strategy: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Greece, Germany, Hungary, Ireland, Latvia, Lithuania, Poland, Portugal, Romania, the Netherlands, Slovenia, and Slovak Republic.

which will ease the networking of centres of expertise across Europe and the creation of European Reference Networks.

3.2.2. European Reference Networks for rare diseases

As a means of organising care for the thousands of heterogeneous rare conditions affecting scattered patient populations across Europe, the creation of European Reference Networks (ERNs) is foreseen by the Council Recommendation on an Action in the Field of Rare Diseases and more recently in the Directive on the application of patients' rights in cross-border healthcare. ERNs, as networks of highly specialised healthcare providers from different MS, are of particular relevance to the field of rare diseases. These structures will aim to improve knowledge on rare diseases, facilitate the mobility of expertise, and allow Member States to provide highly specialised services of high quality for patients where this would have been impossible without European networking.

The European legislative texts listing the criteria and conditions that healthcare providers and the ERNs should fulfil, as well as containing criteria for establishing and evaluating ERNs have been adopted in 2014 [14] and are in line with the recommendations of the EUCERD in the field, issued in 2013, concerning the specificities of ERNs for rare diseases [15].

The EC is currently in the process of defining the designation, assessment and evaluation processes prior to launching the first calls for ERNs. The rare disease community hopes that, over time, all RD will be represented by ERNs in a step-wise manner: a discussion is currently underway at the Commission Expert Group on Rare Diseases concerning the best grouping of diseases as only a limited number of ERNs will be designated. Due to the complexity of rare diseases, these networks should link centres of expertise as well as other stakeholders involved in the care management of the patients such as specialised health and social care providers, patient groups, research groups and diagnostic laboratories.

Currently, a number of non-designated networks exist in the field of rare diseases at European level, of which the experiences have fed into the reflection process at European level, including the EUCERD Recommendations on ERNs for rare diseases. These networks, some of which have received European financing, are mostly based on collaborations between personal experts and their activities are extremely heterogeneous, varying greatly depending on the disease/group of diseases covered [16].

3.3. Adequate identification and coding of rare diseases

The International Classification of Diseases (ICD) is used worldwide and by a range of stakeholders, in particular for coding activities within healthcare systems. Most rare diseases are absent from ICD10, the current version of the classification, and those with a specific code are often misclassified. As a result, morbidity and mortality due to rare diseases are invisible in health information systems. Improved codification for rare diseases is cited as a priority in the Council Recommendation on an action in the field of rare diseases. Having codes for each rare disease would help health authorities obtain a better knowledge of healthcare pathways and of their impact on specialised health care services as well as on a budget planning for health and social services.

To ensure that most rare diseases will have a code in the next edition of ICD (ICD11), expected in 2017, the EC has supported the ICD revision process.[1] In the current beta version [17] of ICD11, over 5000 rare diseases are listed. Although great efforts have been made to integrate rare diseases into the next version of ICD, a solution is needed to ensure that rare diseases are coded adequately as soon as possible, as the implementation of ICD11 may not happen immediately after adoption by the World Health Assembly.

[1] Through two consecutive Joint Actions (No 2008 22 91 and No 2011 22 11).

Orphanet [12], the rare disease and orphan drug database, gives free access to a nomenclature of rare diseases, fully aligned with ICD10, ICD 11 (beta version) and other nomenclatures (SNOMED-CT, MeSH, HPO, MedDRA and OMIM). The EGRD proposes in its recommendations on ways to improve codification for rare diseases [18], that countries consider the use of Orphacodes to complement existing coding systems when no specific code exists for a rare disease. This approach is currently being piloted in France and Germany. As Orphacodes are aligned with the next version of ICD, when ICD11 is implemented, the transition to the new system will be seamless. A working party of the majority of Member States who have expressed their interest in this approach is also being created in order to share experiences concerning the implementation of Orphacodes in health information systems. A master file aligning Orphacodes and all ICD national extensions is foreseen to ease the process.

In addition to the promotion of Orphacodes, another initiative is gathering speed: the International Consortium for Human Phenotype Terminologies (ICHPT) was launched in 2012, bringing together the different terminologies in the field of rare diseases, with the aim to decide upon a set of core terms representing main phenotypic anomalies encountered in the field of rare diseases to be published and recommended for use. ICHPT will provide a mapping between the core set of terms in HPO, PhenoDB, Orphanet, Elements of Morphology, POSSUM, SNOMED, MeSH, and MeDRA. These terms are also recommended for inclusion in ICD11 and SNOMED. This initiative will hopefully effectively harmonise data and improve the interoperability of databases and thus accelerate research in the near future.

3.4. Research and development

There is a great need for research and development in the field of rare diseases as, so far, most patients' medical needs are not being met. The rare disease field is considered to be an area which requires specific initiatives to attract academic and industrial interest. In addition, experts are very rare. Rarity has an impact on research and R&D, in the form of a number of bottlenecks: a lack of necessary collaborative efforts, limited access to platforms, the need for alternative clinical trial designs, and a limited number of patients for clinical research, as well as the challenge accompanying the use of innovative approaches.

The field of rare diseases, however, presents many opportunities to drive forward research and R&D in general: for example, rare diseases were instrumental in mapping the human genome and in cloning genes, as most rare diseases are Mendelian disorders. There is a high level of interest in the biomedical research community to dissect genetic mechanism, which translates into an improvement in testing possibilities for many rare diseases and a better understanding of common disease mechanisms. However, the natural history of rare diseases, in contrast, is often poorly understood due to the obstacle presented by the inability to collect sufficient data for studies due to the rarity of these diseases. A lack of interest in this stage in research is compounded by the current difficulty in using medical records in health information systems due to the inadequate codification of rare diseases in ICD10. Systematic data collection only takes place for a few rare diseases, which presents an obstacle to the development of therapies and good practice guidelines.

As previously mentioned, the field of rare diseases can drive forward research and R&D in general as rare diseases are models for common diseases: as most rare diseases result from a dysfunction of a single pathway due to a defective gene, understanding the impact of this defect yields insights into complex pathways in, generally, multifactorial common diseases. Therefore, promotion of rare disease research is beneficial for the wider scientific community. This interest has translated into the involvement of the pharmaceutical and biotechnology industry in developing new treatments for unmet needs: both innovative and classical approaches can be efficient in treating rare diseases.

3.4.1. Research projects

Research in the field of rare diseases is one of the priorities of the Council Recommendation: it encourages European countries to work at national and community levels to include provisions aimed at fostering research in their national plans/strategies for rare diseases, to identify needs in all areas of rare diseases research, and to foster the development of and participation in cooperative research projects on rare diseases at European level.

At national level, very few European countries currently have specific funding programmes for research in the field of rare diseases, although some specific calls are often funded through funds raised by charities and patient organisations. The national rare disease research carried out in most European countries comes from the general research funding programmes.

At European level, The EC Directorate General for Research and Innovation has included rare diseases as a priority area since the 1990s within the EU research programmes [19]. From 2007 to 2013, around 120 research projects related to rare diseases were financed in the health theme, with an EU contribution of €620 million [4]. The Orphanet database contains around 5700 ongoing research projects for around 2100 rare diseases taking place in EU and surrounding countries participating in the Orphanet consortium [4].

One of the funded initiatives is the ERA-Net for rare diseases research entitled, E-Rare [20]. This consortium of research-funding bodies in 13 European and associated countries (plus 2 observer countries) has launched annual joint transnational calls since 2007 for collaborative and multidisciplinary research projects. The initiative has proved to be a success, with a high rate of proposals received each year in relation to the available funding.

In Horizon 2020 [19], the Framework Programme running from 2014 to 2020, the EC has renewed its engagement in the field of rare diseases, with funding earmarked for the continuation of E-Rare's activities and projects aimed at new therapies of rare diseases. Through its new research programme, the EC will support the objectives of the International Rare Disease Research Consortium (IRDiRC) [21] established in 2011 at the initiative of the Commission and the US National Institutes of Health. This consortium of around 40 funding bodies and organisations from Europe, North America, the Middle-East, Asia and Australasia and researchers aims to achieve the objective of 200 new therapies and diagnostic tools for most rare diseases by 2020.

3.4.2. Disease registries

Patient registries are a key aspect of national plans/strategies for rare diseases and are cited as a crucial source of information on rare diseases, in terms of basic and clinical research as well for epidemiological and public health purposes, to be supported at national and European levels in the Council Recommendation. Patient registries are a key tool for gathering the scarce knowledge relevant to rare diseases so as to improve the understanding of these conditions and the treatment available to patients, as well as the planning of healthcare services for these diseases. In January 2014 there were around 640 disease registries in Europe registered in the Orphanet database, of which 40 were European (many of which have been supported by EU financing), 74 were international, 446 were national, and 77 were regional [22]).

At the national level many countries are considering in the scope of their national plans/strategies the best way to collect data relative to rare disease patients, and at the Community level the EC is in the process of establishing a European Platform for Rare Disease Registration. The EUCERD adopted a set of Recommendations on Rare Disease Patient Registration and Data Collection [23] in 2013 with the aim of setting down the consensus reached to date and to guide all stakeholders at this crucial moment in the collective reflection on the topic. These recommendations are also feeding into discussions on data collection and registration underway at international level in the working groups of the IRDiRC, notably concerning interoperability and pooling of data for research purposes.

3.5. Therapies for rare diseases

The EU Regulation on Orphan Medicinal Products adopted in 1999 was the first European policy text in the field of rare diseases. The Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent or diagnose rare diseases; without such incentives, it is unlikely that products would be developed for these diseases as the cost of development and marketing would not be recovered by sales. The incentives proposed by the legislation aim to assist sponsors receiving orphan medicinal product designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients. The designation is granted if the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 000 persons in the EU when the application is made, and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the EU, or if such method exists, that the product will be of significant benefit to those affected by that condition. The Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) provides opinions on designation applications which are then adopted by the EC.

At the end of 2013, more than 1234 positive opinions for orphan product designations had been adopted by the COMP from the 1798 applications received since 2000 [24]. Eighty-five orphan designated products had received market authorisation by the end of 2013 [24]. The incentives provided by the Regulation have thus resulted in the development and marketing of medicinal products for rare diseases which would perhaps not have been so without such an initiative.

However, although these products are technically available in all European countries as they have been accorded EU market authorisation by the EC, they may not be accessible. The accessibility of orphan medicinal products varies from product to product and from country to country, depending on the price of the product and whether or not the product has been launched on the market in a particular country. Indeed, one of the main factors limiting access to new orphan medicinal products in the EU is no longer market authorisation, but Health Technology Assessment (HTA). Two initiatives have been taken in this field at European level which aim, ultimately, to improve access to Orphan Medicinal Products. The first is a set of recommendations issued by the EUCERD on improving informed decisions based on the clinical added value of orphan medicinal products information flow (2012) [25]: this information flow would consist in earlier dialogue between interested parties including HTA agencies for them to communicate very early on in the process the data requirements necessary for an assessment of the clinical added value of a given drug to be made. The second initiative is the pilot projects supported by the EC to develop a mechanism of coordinated access to orphan medicinal products (2013) [26].

3.6. Patient organisations

The key role played by patient organisations in the empowerment of patients with rare diseases and the necessity of patient involvement in the rare disease field is underlined by the Council Recommendation. At the end of 2013, around 2500 disease-specific patient organisations were registered in the Orphanet database [4]. National alliances of patient organisations have been established in most European countries to provide patients with a common voice and the presence necessary to have an impact on national policy, notably in the development of national plans/strategies for rare diseases. The Member States where National Alliances have been established include: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden and the United Kingdom.

At European level, Eurordis [27], the non-governmental alliance of patient organisations and individuals active in the field of rare diseases,

unifies the voice of rare disease patients in Europe since 1997. EURORDIS is a key actor in the rare disease field and its representatives are actively involved in the rare disease activities of the EC and the European Medicines Agency. EURORDIS runs the Council of National Alliances of Rare Disease Patient Alliances, which brings together national representatives of rare diseases to work together on common European and international actions.

EURORDIS also initiated in 2008 the annual Rare Disease Day, which takes place on the last day of February. This event aims to raise awareness of patients, families and carers living with rare diseases through events organised at national level by rare disease patient alliances, and coordinated at international level by EURORDIS. The day has been adopted across Europe and across the globe, giving momentum to rare disease policy and advocacy.

3.7. Information services

A number of initiatives have been taken to improve the availability of information concerning rare diseases for professionals, patients, and policy makers alike. Due to the rarity of these diseases, the scarce knowledge concerning many rare diseases, and the rare and scattered expertise in this field, a European-level, concerted approach is essential.

At European level, Orphanet, the rare diseases and orphan drug database, is supported by the EC with the support of Member States. In addition, there are two European initiatives to improve communication about rare diseases and activities in the field: a dedicated newsletter, OrphaNews [5], and a State of the Art of Rare Diseases report [29], providing a comprehensive overview of rare diseases activities at European and Member State level. At Member State level, Orphanet national teams collect information concerning expert services in their country for inclusion in Orphanet [12], and some countries have additional rare disease information centres and/or helplines where patients and professionals can seek information and advice concerning rare diseases.

3.7.1. Orphanet

Orphanet [12] is the reference portal for information on rare diseases and orphan drugs in Europe. Established in 1997 by the French Ministry of Health and the INSERM (French Institute of Health and Medical Research), the database and web portal have been supported by the EC since 2000 through a variety of funding mechanisms. To resolve the issue of information dispersion, Orphanet provides direct online access to an inventory and encyclopaedia of rare diseases. Orphanet attributes a unique identifier (Orphacodes, 3.3) to each disease and places them in a polyhierarchial classification of rare diseases. Orphanet provides expert validated information on expert services in its 37 partner countries with the input of national partner teams. These services include expert centres, clinical laboratories, research projects, registries, biobanks, and patient organisations. An inventory of orphan drugs is also maintained. Orphanet is available in 7 languages (English, French, Spanish, German, Italian, Portuguese, and Dutch).

To support policy makers, Orphanet regularly publishes reports in a collection entitled 'Orphanet Report Series', including lists of rare diseases with their prevalence [30,31], lists of orphan drugs in Europe [28], and lists of rare disease registries in Europe [22]. A number of Orphanet datasets are also directly accessible in a number of re-usable formats via Orphadata [32] in order to ensure the dissemination of the Orphanet nomenclature (3.3) of rare diseases and maximise the use of Orphanet's data for research and policy-making purposes.

3.7.2. Helplines

To provide information on rare diseases and services at national level, rare disease specific helplines and centres providing information on rare diseases have been established in some European countries, often at the initiative of patient organisations. In some countries, support is provided to these services through national rare disease plans/strategies.

3.7.3. OrphaNews

OrphaNews [5] is the bi-monthly e-newsletter of the rare disease community, co-financed by the EC. With over 15 000 subscribed readers, the newsletter is a key dissemination tool within the rare disease community. OrphaNews provides updates on the latest political, regulatory, and scientific developments in the field of rare diseases, gathered from a systematic review of the literature and information submitted by national contact points across Europe. The newsletter is available in English, French and Italian.

3.7.4. Report on the State of the Art of Rare Diseases Activities in Europe

Since 2010, the publication of an annual report on the State of the Art of Rare Disease Activities in Europe [29] has been supported by the EC. This multivolume report provides information concerning the state of the art of activities at both European and Member State levels, in particular the advances made to date in the implementation of the Council Recommendation on an Action in the field of rare diseases, notably the elaboration and implementation of national plans/strategies for rare diseases at national level. Elaborated with the input of stakeholders at national level with the help of the members of the Expert Group on Rare Diseases, the report provides a transversal view of the rare disease field and its evolution over the past few years.

4. Conclusions

Great strides forward have been made from 2000 onwards to improve care for patients through the rare disease related policies implemented at European and national levels. The Regulation on Orphan Medicinal Products has led to the development and marketing of over 80 new therapies for rare diseases. The Council Recommendation on an action in the field of rare diseases has encouraged Member States to put into place plans and/or strategies to structure their policies in the field of rare diseases and the majority of European countries have now adopted a plan/strategy with the remaining countries in an advanced stage of elaboration of their policies. The provision of centres of expertise for rare diseases, improved codification for rare diseases and rare disease patient registries are key measures of these plans. The EC is supported by an Expert Group on Rare Diseases which provides key recommendations to the EC and European Member States to ensure that the political approach at European and national levels is cohesive and based on established multi-stakeholder consensus. The Directive on Cross-Border Healthcare is opening new possibilities for the exchange of expertise in the field of rare diseases through the creation of European Reference Networks. Research into rare diseases is being boosted by investments made by the EC in rare disease related projects that promote European research collaborations. The International Rare Disease Research Consortium has been launched to reach the ambitious goal of developing 200 new therapies for rare diseases and establishing means to diagnose most rare diseases by 2020. The availability of information on rare diseases has been improved thanks to the Orphanet database, which provides expert-validated, free, on-line information concerning rare diseases and orphan medicinal products accessible to all audiences. Finally, the implication of patient associations in all of these various areas means that patients' voices are heard and that the cited policies translate into improved care for patients. Much has been achieved in the 15 years following the first European policy in the field of rare diseases, above all the creation of a cohesive and dynamic multi-stakeholder community; however many challenges remain to be surmounted in a particularly tense economic climate. Despite these economic difficulties, it is hoped that the European experience will serve other world regions in developing their own approaches in the field of rare disease policies to improve care for patients.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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