Update on 2004 Background Paper
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Background Paper 6.19
Rare Diseases

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Abbreviations

COMP, Committee on Orphan Medicinal Products
DALY, Disability Adjusted Life Years
EMA, European Medicines Agency
EPPOSI, European Platform for Patients’ Organisations, Science and Industry
EU, European Union
EuroBioBank, European Network of DNA, Cell and tissue banks for rare diseases
EUROCAT, European network of population-based registries for the epidemiologic surveillance of congenital anomalies
EURODIS, European Organisation for Rare diseases
EUROSTAT, Statistical Office of the European Communities
FDA, Food and Drug Administration
ICD, International Classification of Diseases
ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
NIH, National Institutes of Health
NORD, National Organization of Rare disorders
ODA, Orphan Drug Act
OOPD, Office of Orphan Products Development
ORD, Office of Rare Diseases
ORPHANET, database dedicated to information on rare diseases and orphan drugs
PKU, PhenylKetonUria
QALY, quality adjusted life years
SME, Small and Medium-sized Enterprise
USA, United States of America
WFH, World Federation of Haemophilia
WHO, World Health Organisation
Executive Summary

A disease is considered rare when it affects one person out of 2 000 or less. They are between 5 000 and 8 000 rare diseases, most of them genetic. A very rough estimate would be that in the world, one person out of 15 could be affected by a rare disease, this represents 400 million people worldwide of which 30 million Europeans and 25 million Americans. Rare diseases are serious chronic diseases, and are often life-threatening. While most genetic diseases are rare diseases, around 20% of rare diseases are not caused by genetic defects. There are very rare infectious diseases for instance, as well as auto-immune diseases and very rare poisonings. To date, the cause remains unknown for most rare diseases. This makes rare diseases truly a global health issue. In recent decades, considerable attention has been paid worldwide to stimulate the research, development and marketing of medicinal products for rare diseases. In the United States over 400 products have been approved as therapy in more than 200 rare diseases indications and in EU over 70 products for around 45 indications. Many orphan medicinal products are innovative, biotechnological products. Apart from treatments coming available, the introduction of various (research) programmes and networks has advanced understanding and diagnosis of rare diseases as well.

Despite this positive development overall the rare disease burden continues to persist. This persistence is due to lack of knowledge/training, lack of or delayed diagnosis, limited disease understanding, lack of treatment, and lack or limited access to therapy or medical care. Being a complex and heterogeneous mosaic of an estimated 5 000-8 000 conditions, it has become clear that the research need can differ considerably between groups of rare diseases:

Lack of disease understanding: need for fundamental research into disease process

For many rare diseases basic knowledge, like cause of the disease, pathophysiology, semiology, natural course of the disease and epidemiological data is limited or worse, missing. This significantly hampers the ability to both diagnose and treat these diseases. To address this challenge public funding of fundamental biomedical research into the disease process is necessary both at national and at international/European level. While only a small number of pharmaceutical companies are engaged in investing in fundamental research for rare diseases, public-private partnerships are key in view of new therapy development.

Patients with rare diseases are scattered across countries with the consequence that medical expertise on each of these diseases is a scarce resource. Most physicians will never heard of most rare diseases and even less have a chance to diagnose an affected patient. Fragmented knowledge about such diseases, and often limited access to research material (biological samples, mice models, etc) means it is critical that investments in fundamental research go hand-in-hand with investments in dedicated infrastructure and international networks (biobanks, registries, networks of expertise etc). Where needed, these networks can also provide effective medical education and opportunities to train health professionals on rare diseases.

Equally important is the availability of an an appropriate and internationally recognised rare disease classification system which will help generate reliable epidemiological data. Such a system would provide a useful basis for further research into the natural history and causes of rare diseases, allows monitoring of safety and clinical effectiveness of therapies and
measuring quality of care. Several systems are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification, OMIM (Online Mendelian Inheritance in Man) and SNOMED CT (Systematised NOmencature of Medicine – Clinical Trials). Each system has its advantages and disadvantages, and important questions remain unanswered with regard to funding and maintenance of such a system.

Translation of disease understanding into product development or healthcare innovation is hampered

Ongoing fundamental research into the disease process (etiology, genetics, pathophysiology, natural history, etc) will result in more targets for pharmaceutical intervention or healthcare innovation for rare diseases. It can enable the development of new molecules, it also allows researchers to revisit existing drug libraries with fresh knowledge, or to repurpose well known molecules for a specific rare disease. An analysis of designated and approved orphan medicines in the USA and EU revealed that treatment of rare diseases were mainly developed in the field of oncology followed by metabolism. The translation of research into product development or healthcare innovation is not happening equally across all disease categories. It is important to understand the factors that are responsible for this imbalance and the role of a persisting limited interest from industry in certain disease areas. Public funding of translational research, including proof of concept studies, might act as a catalyst to translate rare disease research into the development of new medicines. Making a disease easy to diagnose at an early stage will allow the development of prevention strategies that even in the absence of a underlying treatment can have a significant positive impact on a patient’s life. Diagnosis and prevention strategies represent important tools in reducing the burden of rare disease. Phenylketonuria (PKU) is a classical example where newborn screening allows successful therapeutic intervention through a strict diet or through sapropterin dihydrochloride (Kuvan®) in conjuction with diet that dramatically modify the patients prognosis.

For some rare diseases, translation of research into product development or healthcare innovation has taken place, but further development is hampered.

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, like asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the task. Problems include the small number of patients, the logistics involved in reaching widely dispersed patients, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres.

Clinical trial-funding programmes (e.g. FDA Orphan Products Grant Program, EU Seventh Framework Programme (FP7)) remain essential for orphan drug development. Such programmes are especially important for rare diseases that appear less attractive for the pharmaceutical industry. Critical for marketing authorization and reimbursement is the acceptance of the evidence generated during the drug development. Due to the high medical need, a treatment can become available at an early stage where evidence is robust but limited. This represents a significant hurdle for some methodological assessments and developing alternative methods in small and very small populations is desirable. Similar to fundamental research, large multidisciplinary networks should be funded to stimulate
collaboration between all interested parties and bring together medical experts, reference centers, and patients’ groups for rare diseases. This infrastructure is necessary for performance of clinical trials for rare diseases and subsequent monitoring of the newly authorized products.

A whole new generation of more targeted therapies, like stem cell therapies, gene therapies or therapeutic gene modulations (exon skipping, antisense drugs, RNA interference) is in development and new products are becoming available. To allow these targeted therapies for smaller patient groups to become more common practice in the future, it is critical to continue funding the research and development of these highly innovative therapies through specific budgets or public-private partnership (PPP) programs. The first clinical proof of concept study of alipogene tiparvovec (Glybera®), the first gene therapy product approved in the EU, was partially funded through a translational research programme of the Netherlands Organisation for Health Research and Development (ZonMw).\[^{7128}\]

The use of optimized delivery methods (such as controlled or site-specific delivery) for existing orphan drugs could be of significant benefit for patients with rare diseases. These methods entail an improved pharmacokinetic profile of existing orphan drugs, and consequently an improved efficacy, safety profile or convenience for the patient. Despite these apparent advantages, innovative drug delivery systems remain underused in the area of orphan drugs. The ability to measure the added value these innovative drug delivery methods bring to patients and/or the health care system are critical to justify the additional developments costs for industry and the willingness for payers to fund the treatment. Examples of innovative drug delivery systems are: alternatives for intravenous administration, controlled delivery systems, and site-specific drug delivery.

Another opportunity for research in pharmacological intervention for rare diseases is to pursue the development of molecules that are running out of patent protection, but have demonstrated potential with a favorable benefit/risk ratio for treating a rare disorder. This is known as drug repurposing. The advantage is that more is known about these molecules and that knowledge can be leveraged in a new development programme.

Although the main focus of this chapter is on developments in Europe and the USA, the aforementioned research initiatives to improve treatment and care of rare diseases have the potential to make a difference in the lives of rare disease patients around the world.

Ultimately the continuous support of human society to allocate resources to more vulnerable patient population is critical for research efforts to bear fruits and for new treatments to benefit patients.

CONCLUSION

In the area of rare diseases, there are many opportunities for the EU to build on the successful programmes, projects and networks that have been supported so far. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure (e.g. registries) as well as provision of disease-related information at EU level and beyond (guidelines, diagnosis, patient experience)
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- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase rare disease understanding
- Incentives for development of therapeutics (e.g. clinical trial-funding programmes)
- Assessment methods adapted to small and very small patient populations (e.g. marketing authorisation and reimbursement).

In addition, more support is needed for:
- Translational research to increase translation of disease understanding into drug development or healthcare innovation (e.g. NIH bench-to-bedside grants)
- Innovative diagnostic methods of rare diseases to enable early intervention
- Research, infrastructure as well as implementing guidelines for medical and psychosocial care for rare diseases. This would be especially beneficial for those patients for whom underlying treatment is not yet available.
- Incentives for development of preventive strategies and validated diagnostic techniques
- Incentives to leverage existing knowledge and optimize the use of existing drugs (innovative drug delivery systems and drug repurposing).
- Giving easy access to available healthcare (diagnostic, medical, pharmacological or other types of care) to patients regardless of where they live.
1. Introduction

In 2004, Warren Kaplan and Richard Laing authored a report called Priority Medicines for Europe and the World. Within the report there is a section on Orphan Diseases and in addition there is an extensive background paper written by Sonja van Weeley and Bert Leufkens. (http://archives.who.int/prioritymeds/report/background/rare_diseases.doc) This 2013 background paper builds on this previous work.

Terminology concerning, orphan, rare and neglected diseases has evolved when the previous background report was published. In the 1980s and 1990s particularly in the USA, the term “orphan diseases” was commonly used to designate diseases that because they were only affecting a small population, saw no investments to find a diagnosis and a cure. Recognizing these facts led to ground breaking legislation. In the late 1990s the term “neglected diseases” was promoted which referred to tropical infectious diseases that existed in substantial numbers in remote poor areas of low income countries and hence suffered from the same lack of investments. These diseases are the subject of another background paper (Chapter 6.9) and are not addressed in this background paper. Rarity is the key concept on which the orphan diseases definition rests, rarity either in terms of absolute numbers of patients in the USA or in rates of prevalence in Europe and other countries. This mean that all types of diseases below a certain frequency threshold regardless of their etiology, symptoms or age of onset are covered by the definition. The definition clusters a mosaic of diseases like genetic disorders, rare cancers, autoimmunological disorders or infectious diseases. Today the term “rare diseases” is preferred and used in existing legislation. The term incorporates orphan diseases. This background paper on rare diseases should be considered as the successor to the 2004 background paper on orphan diseases. For medicines, the term orphan drugs is used in the USA and in Europe the regulation is talking about orphan medicinal products.

Rare diseases are a complex and heterogeneous mosaic of an estimated 5 000-8 000 conditions.1 For many of these diseases we do not know what the appropriate medical interventions are. A rare disease is, according to the European definition, a life-threatening or chronically debilitating condition from which not more than five persons per ten thousand citizens in the European Community suffer. 8 In other regions, a somewhat different definition is used, e.g. in the USA a disease is called rare when less than 200 000 inhabitants suffer from this disease. It is estimated that about 30 million Europeans in 27 EU-countries and 25 million Americans suffer from a rare disease.1

While medicine was making striking progress in understanding pathology and in developing evidence based treatments for more common diseases, patients suffering from rare diseases were left behind underrecognized, non diagnosed or with limited treatment options. Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients with more frequently occurring disorders (Regulation EC 141/2000; preamble 7, article 3.1b).9 Therefore, more attention has been paid worldwide over the last few decades to stimulate the research, development and bringing to the market of orphan medicinal products. "Orphan" drugs are medicinal products intended for the diagnosis, prevention or treatment of rare disorders.
Examples of rare diseases

Some rare diseases are actually known to the general public. Examples of the best known rare diseases may be cystic fibrosis, sarcoidosis, haemophilia, phenylketonuria (PKU) and severe acute respiratory syndrome (SARS). But in general, most names of rare diseases are totally unknown to the general public like primary ciliary dyskinesia, Darier disease, erythropoietic protoporphyria, Smith-Lemli-Opitz syndrome, Usher syndrome, alkaptonuria and many others.

Sometimes, rare diseases are especially frequent within a region or a specific ethnic group. For example thalassaemia is rare in Northern Europe but more frequent in the Mediterranean area and Gaucher type 1 disease is most prevalent within the Ashkenazi Jewish population.

Diseases may be rare in a specific area (e.g. Western Europe) whereas it is not rare in another. A typical example of this are infectious diseases like certain types of tuberculosis and malaria. Populations migrations will also influence the incidence and prevalence of diseases. For example nowadays a haemoglobinopathy typical for African-like sickle cell anaemia, is becoming more frequent throughout Europe.

Rare diseases can be grouped by affected organ systems or other pathological characteristics e.g. neuromuscular diseases, inborn errors of metabolism (like lysosomal storage disorders, peroxisomal disorders and mitochondrial disorders), chromosomal disorders, rare forms of cancer, etc.

Specific legislation has been set up in various jurisdictions across the globe to provide incentives to attract investment in Research & Development and marketing for orphan medicinal products.6,10

In the United States over 400 orphan medicinal products for more than 200 indications and the EU over 70 orphan medicinal products for more or less 45 indications have been approved as therapy for a rare disease.3,4,11 These numbers demonstrate that introduction of specific orphan drug legislation has been successful in stimulating orphan drug development and making therapies for patients with rare diseases available. Apart from pharmacological treatments coming available, the introduction of various (research) programmes and networks has advanced understanding, diagnosis and quality of care of several rare diseases.12,13,14,15

A recent special Eurobarometer focussed on European awareness of rare diseases revealed that “Europeans have a relatively accurate understanding of what rare diseases are but detailed knowledge and awareness remain low”. Moreover, in the same survey strong support for policy initiatives linked to rare diseases at both national and European level was expressed.16

However, despite the growing number of approved orphan drugs, enhanced rare disease understanding and improved public awareness of rare diseases in the last the decade, many gaps remain. In this background paper, we will present the need for additional initiatives to develop pharmacological interventions for the unmet medical needs and to make them
equally accessible to the biggest number of patients with a rare disease. We will also touch upon the need for health care innovations and their implementation in clinical practice. Both ways may progress at different speed but are complementary and critical to steadily improve the quality of life of rare disease patients.

Although the main focus is on developments in Europe and the USA, rare diseases are not confined to Europe and the USA. Rare diseases affect people all over the world, and are a true global health issue. Additional initiatives to improve treatment and care of rare diseases have the potential to make a difference in the lives of rare disease patients around the world.

2. **What Is the Size and Nature of Disease Burden?**

According to the European definition rare diseases are not only rare but also life-threatening or chronically debilitating conditions. An estimated 80% of rare diseases have a genetic origin, being either monogenic or polygenic. The other rare diseases may for instance be rare infectious diseases, rare cancers or rare auto-immune diseases. The 30 million Europeans and 25 million Americans suffering from a rare disease coincide with six to eight per cent of the total population.1

The reliability of epidemiological data has improved, but remain inadequate for most of the rare diseases to give firm details on the number of patients with a specific rare disease.17,18 In 2013 the impact and burden of disease is beginning to receive more attention from investigators in public health and are better funded at national and European level.

However today we still miss reliable quantitative data for the burden of disease even if it is generally known that people with a rare disease can suffer significantly.19,20,21 Most rare diseases manifest during childhood; about 30% of affected children die during infancy, and the health and economic burden on survivors can be tremendous.21 In 2002, a retrospective survey by Dionisi-Vici et al. showed that the incidence of inborn errors of metabolism was 1:6 200 in newborn babies in Italy20 and that only 11% reached adulthood. The authors concluded that inborn errors of metabolism constitute a highly heterogeneous category of rare diseases, representing a relevant cause of morbidity and mortality in childhood.

For some monogenetic rare diseases not only the burden for the patients themselves but also in some regions the burden for the society is significant, like for thalassemia and sickle cell anaemia.19

Also childhood cancers are rare diseases with potentially dramatic outcome. One estimate that in European countries, one out of 500 children are diagnosed with cancer before the age of 15.21 As epidemiologic information on rare cancers was scarce, the project Surveillance of Rare Cancers in Europe (RARECARE) was funded by the EU and ran between 2007 and 2010.22,23 The aim of the project was to provide estimates of the incidence, prevalence and survival of rare cancers in Europe. First estimate of the rare cancer burden is that about 4 300 000 patients are living today in the European Union with a diagnosis of a rare cancer, 24% of the total cancer prevalence.
In particular for rare cancers, but also inborn errors of metabolism a considerable number of Orphan Medicinal Products (OMPs) are in development or have been approved. Although perhaps coincidentally, the availability of epidemiological data for these groups of diseases may have contributed to this development.

The research focus is not only on groups of rare diseases, but also on the burden of specific rare diseases, like scleroderma and immune thrombocytopenic purpura. Attention is also paid to the impact of diagnosis on the caregivers well being and on the family economic income. In April 2010 BURQOL-RD, a three year project under the Second Programme of Community Action in the Field of Public Health, commenced. The main aim of BURQOL-RD is to generate an integrated and harmonized set of instruments to quantify the socioeconomic costs and Health Related Quality of Life (HRQOL), of both patients and caregivers. Ten rare diseases were selected with a Delphi approach to run a representative pilot survey in eight European countries. Also included is “a detailed analysis of the services (health and social care) received by people with specific rare diseases in different EU countries, including the identification of formal and informal care”. Results and deliverables will be shared with relevant stakeholders, like patient associations, policy makers and medical community and is anticipated to stimulate the future comparability and monitoring of rare diseases care in Europe.

An appropriate and internationally recognised rare disease classification system is critical in making rare diseases more visible in health information systems and consequently provide reliable epidemiological data from existing and future databases. Potentially, such a system will not only generate reliable prevalence/incidence data, but also constitute a useful basis for further research into the natural history and aetiology of rare diseases. It will also allow the evaluation of the economic burden of the disease, and monitoring of clinical effectiveness of therapies and measuring the quality of care. Moreover, as reliable prevalence data has to be provided to regulatory authorities in order to obtain an orphan designation, increased availability of such data for all rare diseases could represent an important preparatory step in facilitating orphan drug development.

A recent European Union Committee of Experts on Rare Diseases (EUCERD)/Eurogentest workshop identified several classification systems that are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification (Orphacode), OMIM and SNOMED CT. Each system has its advantages and disadvantages. ICD is a widely used clinical tool to register a patient diagnosis using a defined nomenclature. However, specific ICD codes are present for not more than 240 rare diseases (e.g. thalassaemia, cystic fibrosis, haemophilia etc.). Other rare disorders are often summed up as ‘other endocrine and metabolic disorders’. In practice, the existing ICD system cannot be used for specific rare diseases. It is expected that ICD-11 will improve the breadth of coverage, but it will not fully overcome this problem. The SNOMED CT is the most comprehensive disease terminology system. It is intended to be used in electronic health records to code the health status of patients; but as system designed to be comprehensive for common occurrences it has some shortcomings when it comes to rare diseases. In contrast to SNOMED CT, the Orphanet classification system is entirely dedicated to rare diseases and requires acceptance in national health record systems. Finally, OMIM is the standard coding system for genetic phenotypes widely used for that purpose.
Recommendations by the experts present at the workshop were to continue to focus on ICD11 meeting the needs of the RD community as much as possible. Second recommendation was to set up an active collaboration with SNOMED CT to ensure that missing codes are considered for incorporation. Third recommendation was to raise the acceptance of Orphanet and OMIM codes as the standards of the rare disease community. Final recommendation was to “continue cross-referencing OMIM and Orphanet codes with the standard terminologies (ICD and SNOMED CT), as it is a quality-control exercise for all of these terminologies and as it is necessary for navigation from one classification to another.” To provide the rare disease community with tools to navigate from one database to another, the four classification systems have recently been cross-referenced by Orphanet. Further work will be required to improve these different systems of classification.

3. What Is the Control Strategy?

Representing a group of 5 000-8 000 complex and heterogeneous conditions makes the description of a specific control strategy for rare diseases extremely difficult if not impossible. The control strategy for a specific rare disease depends on the nature of the disease (genetic or non-genetic), the knowledge obtained for a specific disease, translation of this knowledge into an effective treatment, diagnostic or preventive tool or some other kind of healthcare innovation. Moreover, various socio-economic and demographic factors also play an important role.

In general, a large group of rare diseases have to be managed through care alone, because no therapy is available. Another group of rare diseases are managed through existing medical treatment combined with care. Finally, with new therapies becoming available a growing group of rare diseases are managed through some form of intervention.

For several (mono)genetic rare diseases prenatal and/or newborn screening is possible. In case a high risk for genetic disorders is known prenatal screening is in many cases possible and performed in clinical genetic centres or in other referral centres. In case of the general population, many countries screen newborns for certain metabolic defects. In this way early diagnosis of the defect can lead to early intervention and preventive care. Despite important technological progress that could facilitate newborn population screening a high variability exist between countries/regions in the type and number of diseases screened. This is mainly due to the lack of data on the cost effectiveness and the ethical implications of the screening strategies.

An effective control strategy for a single disease will depend on a combination of three strategies: an effective early diagnosis, the development of optimal care including preventive care and the availability of a drug or another therapeutic interventions. As explained in the examples below, the importance gained by each strategy will vary per disease.

The impact of early diagnosis is best exemplified by classical phenylketonuria (PKU). This inherited metabolic disease is characterized by an inability of the body to utilize the essential amino acid, phenylalanine, due to a deficiency of the enzyme phenylalanine hydroxylase. Without this enzyme, phenylalanine and other biochemical products accumulate in the
blood and body tissues. The excess phenylalanine is toxic to the central nervous system, and results in mental retardation and other neurological problems when left untreated. When a very strict diet is begun within the first few weeks of life and is well-maintained, affected children can expect normal development and a normal life span. Recently a pharmacological treatment (sapropterin dihydrochloride, Kuvan®) stimulating the residual enzyme activity and lowering the phenylalanine blood levels became available to use in conjunction with a restricted diet. Because of the very positive outcome when children are treated early and well, newborn screening for PKU is carried out in most developed countries.

Haemophilia remains a prime example of a rare disease for which the control strategy in developed countries has had enormous effects on reduction of morbidity, burden of disease and prevention of mortality. Haemophilia is an X-linked inherited coagulation disorder due to a partial or total lack of an essential coagulation factor. Haemophilia A is the most common form, referred to as classical haemophilia, and is the result of a partially or complete deficiency of coagulation factor VIII; haemophilia B is caused by a deficiency in activity of Factor IX. It is a chronic disorder affecting mostly males, characterised by internal bleedings in joints (ankle, knee, elbow, shoulder and hip), in muscles and soft tissue. Without treatment the bleedings causes malformation of the joints and chronic disability. The patients have a low quality of life and usually die in childhood or early adult life.

Diagnosis is carried out via blood tests in which the coagulation factor can be measured and mutation analyses can be performed. Carrier detection and prenatal diagnosis is possible, but not in all cases. Preimplantation diagnostics ((PIGD) gives the possibility to implant unaffected female embryos in the uterus of women who are a carrier for haemophilia, circumventing the possibility of giving birth to an affected child. However, the ethical issues concerning prenatal diagnosis and PIGD have to be taken into account.

Effective treatment for haemophilia has become available in the last forty years and consists of supplementation of the deficient coagulation factor via intravenous administration. In the first decades the coagulation factors were purified from human plasma. From the 1990’s recombinant (genetically engineered) factor VIII or IX have become available and increased safety of administration by eliminating the risk of viral contamination. When patients suffer severely from haemophilia current standard therapy includes treatment with prophylactic intravenous infusions several times a week, and additional infusions for any bleeding which may occur, or for surgery or other invasive procedures. The patients most often treat themselves at home or with help of a family member to prevent bleedings and joint disease. Monitoring of treatment usually takes place in centres of expertise with a multidisciplinary approach. Advisory guidelines have been developed for prevention and appropriate treatment. Currently under development are a number of modified versions of native clotting factors, most of which are longer acting and directed at providing an opportunity for prophylactic infusions to be administered less frequently.

Healthcare innovations and their implementation in clinical practice have proven to be an important way to improve the quality of life of rare disease patients. Cystic Fibrosis (CF) is one example of a rare diseases that has benefited from improved care and symptomatic treatment.
The disease is complex and can lead to many different complications (see Figure 6.19.1 for details). In the 1930s, life expectancy of a patient with CF was less than a year but through increased understanding and improved diagnosis and care, nowadays patients with CF can expect to live into their 30s, 40s and beyond. Medicinal products have been approved for symptomatic care e.g. treatment of bacterial infections or to help clearance of the airways. However, they are part of the overall care of patients that also include diet, exercise, infection control. This total “care” package has contributed considerably in increasing the life expectancy of a CF patient as well as improving the quality of his/her life. Patient organisations, like the CF Foundation (www.cff.org), play a key role in continuously providing patients with relevant information on the current state of care, research as well as which products are in development. The inherited chronic disease affects 70,000 people worldwide. Much is known about the disease manifestations and the natural history of the disease has been modified through optimal and preventive care. The defective gene was discovered in 1989 and more than 900 mutations have been identified. However the first medicine (ivacaftor; Kalydeco™) targeted at the underlying cause of the disease was only approved recently in 2012 for a subset of CF patients presenting the G551D mutation.

As stated in the introduction, specific orphan drug legislation in various jurisdictions has given a significant stimulus to the development of therapies for rare diseases (see next
The American Orphan Drug Act (ODA) was the first orphan drug regulation and came into force in 1983. An important incentive of the ODA for the pharmaceutical industry is the market exclusivity of seven years for products with an orphan designation that have got marketing authorisation. The status of orphan designation qualifies the sponsor of the product for a credit against tax, up to 50 per cent, of certain clinical testing expenses related to the use of a drug for a rare disease or condition and for protocol assistance.

Other regions have followed this policy for rare diseases and developed orphan drug regulations themselves: Singapore in 1991, Japan in 1993, Australia in 1998, and the EU and Taiwan in 2000. Each Orphan Drug Regulation has its own characteristics, both in criteria of a rare disease and in the incentives to stimulate orphan drug development (see Annex A for an overview of various regulations). In EU Regulation No 141/2000 a 10-year market exclusivity period is provided after granting of a marketing authorisation. In addition, protocol assistance, fee reductions, use of the EU centralised procedure for marketing authorisation and incentives for research into orphan medicinal products are included. To benefit from these incentives in the two largest jurisdictions, a sponsor has to apply and obtain an orphan designation for its product from the Food and Drug Administration (FDA) or European Medicines Agency (EMA)/European Commission in the USA and the EU, respectively. Products intended for treatment, diagnosis or prevention of rare diseases that fulfil a set of predefined criteria are eligible for an orphan designation.

Both EU and United States orphan legislation include a definition of the rarity of the indicated disease. In the EU, the first criterion to be fulfilled for designation as OMP requires either that the targeted rare disease does not affect more than five people per 10 000 (= prevalence criterion), or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment (= return on investment criterion). The EU has two additional important criteria that have to be fulfilled. In the EU, an orphan designation will only be provided if the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition (= seriousness criterion). Moreover, the sponsor should establish that there exists no satisfactory method for the diagnosis, treatment or prevention of this condition, or if such a method exists, that the new product will be of significant benefit for those affected by that condition (= significance criterion). What this means is that if an approved product for the indicated disease already exists, the market exclusivity for that product (with OMP status) will end if a so-called follow-on orphan drug has a clinically relevant advantage or a major contribution to patient care. In the USA, a rare disease is defined as a disease with a maximum of 200 000 patients (equivalent to seven patients per 10 000 residents).

4. What Is the Current "Pipeline" of Products that Are to Be Used for these Particular Conditions?

The lists of designated orphan medicinal products in the various regions with specific legislation in place can be considered as the pipeline of pharmacological interventions for rare diseases. These products are investigated further in clinical trials, but have already been
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recognised as potential products for rare diseases. Table 6.19.1 provides an overview of designated and approved orphan medicinal products in USA, Japan, Australia and EU (Status: June 2012).

Table 6.19.1 Designated and approved orphan medicinal products in USA, Japan, Australia and EU (June 2012)

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>OMP Status</th>
<th>OMP Market Authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>2609</td>
<td>403</td>
</tr>
<tr>
<td>Japan</td>
<td>269</td>
<td>173</td>
</tr>
<tr>
<td>EU</td>
<td>1000</td>
<td>70</td>
</tr>
<tr>
<td>Australia</td>
<td>231</td>
<td>62</td>
</tr>
</tbody>
</table>


Note: MA, Market authorisation; OMP, Orphan medicinal product Status, the product has the status of OMP, but its safety, quality and effect has still to be analysed by a committee before the product may be registered.

The overview shows that the introduction of specific Orphan Drug legislation has facilitated the development of therapies for several rare diseases. As reported by Haffner et al. in the decade prior to 1983 fewer than ten such products came to market. The regulations have proven to be an effective strategy to attract the pharmaceutical industry, especially the small biotech industry, to find their niche in rare diseases. According to Haffner, the orphan drug act in the USA allowed the start of a number of USA-based biotechnology companies, like Genentech, Amgen and Genzyme, and the translation of rare disease knowledge into numerous highly innovative rare disorder therapies.

In the last three years we have witnessed a growing interest from larger pharmaceutical companies in orphan drugs and rare disorders. This is best exemplified by the introduction of specific rare disease units, for example at Pfizer, GSK and Sanofi who bought Genzyme in 2011, or by giving them a more prominent position in their business model, such as at Novartis. This growing interest should not be interpreted as a lack of activity by large pharmaceutical companies at all in the field of orphan drugs previously. Most companies have been involved from the start of the legislation and some drugs are indicated for rare diseases without enjoying an OMP status. They might however not have had a visible focus on rare diseases and hence their role has been slightly less prominent than SMEs.

4.1 USA

Since 1983 the Orphan Drug Act more than 2 600 products have been designated as orphan, and more than 400 products have been approved. Braun et al. showed that in the first 25 years of the Orphan Drug Act, 326 products have been approved that target more than 200 rare diseases and really make a difference in the lives of millions of rare disease patients. These products do not target only the more prevalent rare diseases, but also quite a number
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of very rare diseases.\textsuperscript{3} In contrast, in the decade prior to 1983 fewer than ten such products came to market.\textsuperscript{6}

Although in the last decade the annual number of orphan designations has continued to grow, the annual number of orphan drugs that has been approved in the same period remains more or less constant.\textsuperscript{3} Nevertheless, the number of non-orphan drugs approved has declined in the last decade, and consequently the proportion of all drug approvals that are orphan drugs has almost doubled in the last twenty years.\textsuperscript{47} According to Cote\textsuperscript{47}, orphan medicines roughly represent one third of all newly approved drugs and biologics in the USA.

4.2 EU

In the first twelve years (2000-2012) of the EU Orphan Medicinal Product Regulation around 1 000 products were designated as OMP of which 70 have received marketing authorisation.\textsuperscript{11,4} As with the US Orphan Drug Act,\textsuperscript{6,43} the EU Orphan Medicinal Product Regulation is highly appreciated for its role in creating a favourable orphan drug development environment.\textsuperscript{4} Unlike the US, annual approval of orphan drugs in the EU in the last decade has been variable.\textsuperscript{48}

4.3 Japan

In Japan, 269 drugs were designated as orphan drugs for more than 100 diseases and 173 were approved between 1993 and 2012.\textsuperscript{11} In the first six years after the orphan legislation came into force, thirty eight percent of the designated orphan entities were biological in origin. In Japan 32\% of the orphan medicinal products were already approved in other countries when they were designated as orphan drugs in Japan. Ten drugs were developed for the first time in Japan.\textsuperscript{49}

4.4 Australia

In Australia 231 products were designated as orphan drug and 62 of them received a market authorisation in the period between 1998 and 2012.\textsuperscript{11}

5. Why Does the Disease Burden Persist?

Although therapies are becoming available, it is important to understand that the burden of rare diseases continues to persist. Of course, an obvious reason is that the number of therapies coming available is still very low compared with the total number of diseases. Another reason is that many rare diseases are chronic debilitating diseases, that are diagnosed or presented at an early age. Growing older will in general coincide with the same or even a lower quality of life. Furthermore, many of these diseases are genetic and will therefore exist for generations. There are a number of key factors that continue to have an impact on the burden of disease.\textsuperscript{50}
5.1 Lack of knowledge and training

Basic knowledge about diseases, list of available drugs, lists of specialists or consultants specialised in a given disease, are still not widely available in the world. In general, medical doctors and general practitioners are not trained in rare diseases and lack experience. The latter was confirmed in a recent report by the UK think-tank; '2020health'\textsuperscript{55}. Because of the sheer number of diseases (5 000-8 000) and the multiplicity of disease presentations doctors cannot be expected to know the symptoms of the many rare disorders. Most diseases names are unknown to physicians. However, they can develop a sense of urgency that a specific patient with unfamiliar cluster of symptoms and complaints should be referred to a specialist. We can also expect that bioinformatics and computer assisted diagnosis will be tools to help physicians in better recognizing rare ailments.

5.2 Lack of information

Dissemination of information is a key issue in the field of rare diseases. Without information, diagnosis and treatment cannot be improved, research will not continue, the patients are not empowered and there is ineffective use of clinical resources. In 2004 a lack of infrastructure and exchange of information was reported as a considerable hurdle. However, in the last decade, American organisations like NIH, NORD and FDA, and European organizations like EURORDIS, ORPHANET and EPPOSI and various EU programmes (the EU Framework Programmes for Research and Technological Development; the EU Health Programmes) have considerably improved the infrastructure and exchange of information on specific rare diseases or general issues on rare diseases. The organizations and programmes mentioned are examples of good intra- and intercollaboration between the different stakeholders (patients, science, industry, government) and are considered successes of American and European funding.

Orphanet has contributed to the broad worldwide exchange of information on rare diseases. Currently around 5 954 rare diseases are registered on the site.\textsuperscript{56} Similarly, OMIM provides a comprehensive overview of human genes and genetic phenotypes. EURORDIS, a patient alliance, represents more than 510 rare disease organizations in 48 different countries and covers a total of more than 4 000 rare diseases (www.eurordis.org).\textsuperscript{57} Many national alliances and rare disease-specific patients organizations have evolved. These organizations are playing a key role in both providing support to rare disease patients, facilitating access to updated information on rare diseases, exchanging information and networking and stimulating scientific research.\textsuperscript{58} Moreover, they provide patients with a common voice and seriously impact national policies on rare diseases. An example of a national patient organization is VSN (Vereniging Spierziekten Nederland), a patient organization for neuromuscular diseases in the Netherlands which collaborates closely with national and international (such as Treat-NMD) partner organizations.\textsuperscript{59} These networks will require ongoing support as an organisational basis for research and the provision of information.

5.3 Lack or delay of diagnosis

Important factors that contribute to the burden of disease of rare disorders are a lack or delay of diagnosis due to a lack of awareness within the community but also because easy and reliable tests are missing. For several genetic diseases the diagnosis can be suspected by detecting biochemical changes in biological samples (enzyme activity, high or low level of
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specific substances in blood or urine), the genetic defect can then be confirmed by molecular biology techniques. Some diagnosis methods are more invasive and will require organ biopsies. However, for many diseases specific diagnostic tools are still missing partly due to a lack of research and understanding on the pathophysiology of these diseases. In some cases the diagnosis is based only on clinical symptoms or made by excluding other diseases.

Over the last years, major progress in gene identification has been translated into diagnostic testing. These tests are now available internationally, through both the public and private sector genetic testing service. In 1997, Orphanet set up a database of medical laboratories. In 2011, data was collected from 36 countries and funded by the European Commission. Over the past five years, in collaboration with EuroGentest Network of Excellence (financed by the European Commission) information on quality management has been added. In 2011, 1056 laboratories offering tests for 1 811 genes were registered in Orphanet. Tests offered differ greatly between countries, highlighting the need to provide access to services in all EU countries.

These developments are promising, but it is important to understand whether they result in early and confirmatory diagnosis of rare diseases and ultimately improve patient outcome or quality of life. In a survey by EURORDIS in collaboration with 70 European rare disease organisations (EurordisCare2) several aspects concerning diagnosis were compared for eight rare diseases in 16 European countries (5 980 patients). Important findings were that 25% of patients had to wait between five and 30 years from early symptoms to confirmatory diagnosis of their disease. Moreover, before receiving a confirmatory diagnosis, 40% of patients first received an erroneous diagnosis that subsequently led to medical interventions (surgery, medicinal treatment or psychological care). Finally, “the genetic nature of the disease was not communicated to the patient or family in 25% of cases”. This is paradoxical, given the genetic origin of 80% of rare diseases. Most importantly, “the results of the survey highlight the dilemma of rare diseases: lack of information, lack of appropriate medical training, difficulties in accessing care, and as a result, loss of confidence of patients in the health care system and the medical profession”. The aforementioned 2020 health report provides corroborative evidence that “the quality of life of those suffering with rare diseases is severely impeded”. Moreover, the report reveals that wrong or late diagnosis costs considerably more than early diagnosis and consequently requires expensive and invasive medical treatment. This again stresses the already mentioned importance of raising awareness, education, training and the right tools to help physicians in better recognizing rare ailments.

The availability of an effective intervention is a strong incentive to diagnose patients earlier in their disease course. The impact of early diagnosis has been described above for classical phenylketonuria (PKU). Like PKU many rare (metabolic) disorders are expressed early in infancy or childhood. Some of these diseases (e.g. lysosomal storage disorders like Gaucher, Fabry, several type of mucopolysaccharidosis and Pompe) are treatable and as such could benefit from early diagnosis. The introduction of multiplex technologies, in particular tandem mass spectrometry, has the potential of simultaneous multi-disease screening using a single analytical technique. It has already resulted in the inclusion of other genetic metabolic disorders in a number of national newborn screening programmes or pilot programmes. However, as stated in a recent report by the EU Network of Experts on

1 Crohn’s disease, Cystic fibrosis, Duchenne muscular dystrophy, Ehlers-Danlos syndrome, Marfan syndrome, Prader Willi syndrome, Tuberous sclerosis and Fragile X syndrome
Newborn Screening and confirmed by others it also “raises concerns about privacy and autonomy, highlighting the importance of the evaluation of ethical, legal and societal aspects.”62,66,67 Other aspects that have been reported and need to be taken into account are clinical effectiveness as well as cost-effectiveness of newborn screening.68

5.4 Natural history of the disease

For many rare diseases the etiology of the disease and physiopathology remain unknown and/or there is not much insight into the natural history of these diseases.69 There are no animal models available or in vitro and in vivo studies possible. In all those diseases, it is not possible to identify possible pharmacological/therapeutic targets. Very few diseases are well enough understood to start research for an effective treatment.

The absence of knowledge on the natural course, including cause, of a disease makes it difficult for diagnosis, especially when no diagnostic tools are available and diagnosis has to be made clinically. Furthermore, knowledge of the natural course of the disease is critical to develop clinical guidelines by the scientific societies and design valuable endpoints in clinical trials. Disease registries can play an important role in recording the natural history of the disease, for instance for research, epidemiological and post-market studies purposes. In Europe, more and more registries are now available through various initiatives by hospitals, patient organisations, pharmaceutical companies or even a combined effort.70 Orphanet nowadays provides an extensive overview of disease registries in Europe.71 The coverage of the registries reveals that registries exist at regional, national and/or international level. It also appears that registries are mostly located in Western European countries and less in Eastern European countries. Unfortunately, registries are not always compatible with each other and may not use the same coding system. Consequently, this hampers the collection of reliable epidemiological data on rare diseases across registries. Current efforts are undertaken to combine various (national) databases into larger overarching international disease registries.72 An example in this respect is Treat-NMD (Translational Research in Europe – Assessment and Treatment of Neuromuscular Disease), which not only combines many national Duchenne muscular dystrophy registries into one international database but also oversees the sharing of data with relevant stakeholders.73 Treat-NMD was initially established as a EU funded ‘network of excellence’.

5.5 Lack of treatment

As mentioned above specific orphan drug legislation in various jurisdictions has given a major stimulus to the development of therapies for rare diseases. However, recent overviews and studies also indicate that certain rare diseases are favoured. The majority of designated and approved orphan drugs in the first ten years (2000 - 2010) of the EU Orphan Drug Regulation were intended for treatment of rare diseases in the field of oncology followed by metabolism.41 Similar results have been reported for the USA.63 The latter indicates that translation of rare disease research into an orphan drug development is not equally shared between disease classes, which was confirmed by Heemstra et al.74

Designated and approved orphan medicinal products do not only target the more prevalent rare diseases, but also quite a number of less prevalent rare diseases.34 Products are on the market for less prevalent rare diseases, such as tyrosinemia type I (Orfadin®) and N-acetylglutamate synthetase (NAGS) deficiency (Carbaglu®). For other less prevalent rare
diseases, products are in development. Apparently, given the right circumstances orphan drug development for less prevalent rare disorders is feasible. The question is what drives the rare disease research process towards product development.

Heemstra et al. showed that translation of rare disease research into an orphan drug discovery and development programme is more likely for a more prevalent rare disease than a less prevalent rare disease.\textsuperscript{74} The latter was confirmed by Yin who reported that \textit{“the United States Orphan Drug Act has led to a significant and sustained increase in new trials among more prevalent rare diseases, but not for less prevalent rare diseases”}.\textsuperscript{75}

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, such as asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the developers task: too small a number of patients, clinical trial logistics, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres.

Studies have shown that experience in orphan drug development is need for a pharmaceutical company to perform a multinational clinical development programme for an orphan drug that supports a successful marketing authorization application.\textsuperscript{48,76} The same studies also indicated the importance of interaction with the regulatory authorities during development. Regulatory authorities have gained more experience with clinical trials in which a small population have been studied.

Moreover, specific legislation has been implemented in the USA and the EU to allow earlier and faster approval of medicines that treat serious diseases with a high medical need.\textsuperscript{46} Approaches implemented in the USA are fast track, accelerated approval and priority review. The EU has implemented similar approaches: exceptional circumstances, conditional approval and accelerated assessment. Although these approaches are not specific for orphan drugs, OMP easily qualify for these approaches as they treat chronically debilitating or life-threatening diseases that also happen to be rare. It is however really important to realize that orphan drugs do not automatically qualify for the aforementioned approaches.

There is criticism whether these approaches have been effective or optimally used in providing early access of rare disease patients to innovative therapies. In the EU several orphan drugs have been granted approval under exceptional circumstances. However, most approvals were granted in the first years of the EU orphan legislation, which suggests that granting approval of orphan drugs under exceptional circumstances has become more or less exceptional.\textsuperscript{46} Moreover, Boon et al. showed that neither exceptional circumstances nor conditional approval accelerated the approval process for innovative medicines in the EU.\textsuperscript{77} In the USA accelerated approval of therapies for rare diseases has been limited. Only one drug (agalsidase beta; Fabrazyme\textsuperscript{®}) among 73 new chemical entities (NCE) has successfully followed the accelerated approval route.\textsuperscript{78} In their study, Miyamoto and Kakkis build a convincing case that more appropriate use of the accelerated approval route could also have a profound impact on driving therapeutic innovation for rare diseases, in particular ultra-rare ones.\textsuperscript{78} As the authors demonstrate \textit{“better accelerated approval access could reduce development costs by approximately 60%, increase investment value, and foster development of three times as many rare disease drugs for the same investment”}. Through extensive lobbying by numerous stakeholders, including patient organizations, new legislation to allow early
access of orphan drugs in the USA may soon become a reality in the USA (FAST Act, TREAT Act, ULTRA Act). How effective these new legislations will work remains to be determined.\textsuperscript{78}

5.6 Inequity in terms of accessibility of the treatments

A growing hurdle for the successful delivery of new orphan drugs to patients is the uncertain access and reimbursement of orphan drugs after marketing approval. Without access to the approved orphan drugs for the patient, the product has little utility. For various reasons, including pressure on national healthcare budgets and public health policies, access and reimbursement of orphan drugs vary between the individual member countries within the EU.

5.6.1 Public health priorities

A 2007 survey by Eurordis, the European organisation for patients with a rare disease, showed that access to orphan drugs in Europe was highly variable between countries.\textsuperscript{74} Only in four out of 28 countries did patients have access to at least 20 out of 22 orphan drugs a year after approval. The variability in access to orphan drugs may also be the result of other factors: in its 2007 survey report, Eurordis revealed a longer delay for countries with a smaller population. European lower- and middle-income countries are still having problems in terms of access to orphan drugs which would assist in the care for rare disease patients.\textsuperscript{79} A number of orphan drugs are in development by (small) companies that do not have a sales force in all European countries and may consequently need more time to be able to reach smaller markets. Moreover, companies (including large ones) might also voluntarily decide not to market (or to delay the marketing) in various countries (including larger countries).

5.6.2 Pricing and reimbursement

There has been growing debate of the orphan drug field which centre around three key perceptions of the field: the high price of orphan drugs, their inability to meet the standard cost effectiveness threshold and the construct of the system itself which allows companies major benefits from labelling a product as an orphan drug.\textsuperscript{80,81,82,83}

Recently, Roos et al. claimed that the highly praised market exclusivity incentive basically creates a market monopoly that in their view has allowed manufacturers to charge ‘exorbitant’ prices for orphan drugs.\textsuperscript{84} Tambuyzer, in contrast, argued that “if an approved Orphan Medicinal Product (OMP) is currently the only product on the market, it is either because a company was the first to develop a treatment for this disease and competitors have yet to enter the market or because the market is too small to attract competition, rather than because the incentives have created a monopoly”.\textsuperscript{85} Brabers et al. provided evidence that absence of follow-on OMP development is more a matter of time or market size, rather than the creation of a market monopoly.\textsuperscript{86}

A significant challenge may persist in generating evidence in small to very small heterogeneous population. Due to the high medical need, a treatment can become available at an early stage where evidence is robust but limited. In rare diseases it is also not unusual due to the small heterogeneous sample size that clinical significance is greater than statistical significance. This represent a significant hurdle for some methodological assessments that will consider. More research for alternative methods in small and very small populations is
desirable to increase acceptance of the data that can be generated from a limited patient pool in a rather short period of time.

Whatever the reason, a delay in market access of orphan drugs to the European market will be a disincentive for sponsors of potential orphan drugs and hence may reduce the number of new orphan drugs that will be developed in the long term. Consequently, obtaining access and reimbursement for an authorised orphan medicinal product is of great importance for the sponsor and for the patient.

One of the ways forward is to reduce the knowledge and data gap between the regulatory process that evaluate the risk benefit profile and grant marketing authorisation for an orphan drug and the reimbursement process that focus on clinical effectiveness and cost-effectiveness in a local health care system. Steps are undertaken to identify and assess the possible options for the creation of a mechanism for the exchange of knowledge between European authorities and Member States and facilitate the flow of information to support the scientific assessment of the Clinical Added Value of Orphan Medicinal Products (CAVOMP).\textsuperscript{87,88} Finally, a new assessment tool is needed for Member State governments to evaluate a new orphan drug at the time of pricing and reimbursement. Such a system should be adapted and able to consider the peculiarities of the clinical evidence available, the sample size, and the burden of the disease.\textsuperscript{80} From a public health perspective, it should be able to give to these rare patient populations equal access to treatment when it comes to life-threatening diseases and where no other alternative exists for these patients.

5.7 Access to medical care
Focus should not be just on cure but also, or perhaps even more, on (access to) high-level medical care. As mentioned above, for many rare diseases currently no treatment exists. For some rare diseases, a treatment based on the current state of scientific knowledge may not be realistic. Even if a therapy is feasible, drug development still takes around 10-15 years. Compared to drug development, healthcare innovations and their implementation in clinical practice represent a real short term opportunity to improve the quality of life of rare disease patients.\textsuperscript{89}

Bottlenecks in care for rare disease patients have been mentioned as an important burden in daily life. A study in 2003 by the Dutch research institute; Nivel, showed that the quality of life of patients with a rare chronic disease was worse in comparison to more prevalent chronic disorders, both at physical and psychosocial level.\textsuperscript{91} In this study, questionnaires to 206 patients (representing 72 rare diseases) from an existing panel of 2 500 chronically ill patients were analysed. People with a rare chronic disorder experienced more problems in care and daily life than people with more common chronic disorders like cardiovascular diseases, respiratory diseases and diabetes. Forty five per cent had complaints of gloominess, tenseness or anxiety. Finally, almost 25% would like to have emotional support, e.g. from physicians, psychosocial workers or through contacts with fellow-sufferers. Patients with a rare disorder also use more medical care.\textsuperscript{51,90}

A more recent and extensive survey by Eurordis was held to fill the void of the experience and the needs of patients in terms of offer for care by future centres of expertise.\textsuperscript{91} The survey was part of the Rare Disease Patient Solidarity Project (RAPSODY) supported by the European Commission. In the survey patients’ experience and expectations concerning
access to health services were compared for 16 rare diseases in 22 European countries. In total, the study involved 130 patient organizations and 5,995 patients. Important findings were that “the average patient required more than nine different medical services, over the two-year period preceding the survey”. Other difficulties that were mentioned were difficult to impossible access to services (26%). With regard to social services: more than one-third of patients met a social worker with difficulty or could not meet one at all. Social services were rated by half of the respondents as not or somewhat meeting their expectations. Around one third reported that he/she or another member in the family had to reduce or stop professional activity as a result of the disease. Finally, “18% of respondents experienced rejection by a health care professional. The majority of patients reported a reluctance of professionals to treat them due to the complexity of their disease.”

It is expected that the need for access to care will be even higher in some countries. Improving the infrastructure for medical and psychosocial care for rare diseases could diminish the burden of disease for many patients. This would be beneficial for all patients but might be even more critical when there is no short-term hope to find a treatment.

6. Which actions have been/are being undertaken to reduce the rare disease burden?

6.1 Europe

Since 2004, several reports have been issued with detailed information on initiatives and incentives at EU and Member State (MS) level. Focus is on the three European Commission Directorates-General (Health and Consumers; Research and Innovation; Enterprise and Industry) that have a major influence on rare disease and orphan drug policy and other rare disease initiatives. Below we have included a concise description of actions at community (European) level.

6.1.1 Actions at a (European) Community level

For more than two decades, the European Commission (EC) has been addressing the problems of rare diseases, thereby contributing to the reduction of the burden of rare disease patients. An important legislative action that has already been mentioned above has been the introduction of specific legislation to stimulate the development of therapies for rare diseases.

Through its consecutive Programmes of Community Actions in the Field of Health and Framework Programmes for Research and Technological Development, the EU has paid a special attention to rare diseases. Initially, a strong focus existed on exchange of information, networks and funding fundamental research. However, more recently funding

2 alternating hemiplegia, Aniridia, Ataxias, Chromosome 11q disorders, Cystic fibrosis, Ehlers-Danlos syndrome, Epidermolysis bullosa, Fragile X syndrome, Huntington disease, Marfan syndrome, Myasthenia, Osteogenesis imperfecta, Prader-Willi syndrome, Pulmonary arterial hypertension, Tuberous sclerosis and Williams syndrome
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also focussed on translational research and pre-clinical and clinical development of orphan drugs for prevention, diagnosis or treatment of rare diseases.

As stated by the EC on its website\(^9\), focus of actions at Community level is on:
- improving recognition and visibility of rare diseases
- ensuring that rare diseases are adequately coded and traceable in all health information systems
- supporting national plans for rare diseases in EU Member States
- strengthening European-level cooperation and coordination
- creating European reference networks linking centres of expertise and professionals in different countries to share knowledge and identify where patients should go when expertise is unavailable in their home country
- encouraging more research into rare diseases
- evaluating current screening population practices
- supporting rare diseases registries and providing a European Platform for rare diseases registration.

6.1.2 Coordinating activities

An important action by the European Commission has been the launch of the Rare Disease Taskforce (RDTF) in 2004.\(^9\) The RDTF consisted of experts from Member States, representatives of the European Commission (DG SANCO, RTD, ENTR and EUROSTAT), EMA, and WHO-Europe. Their mandate was to improve information exchange between relevant authorities, to contribute to accurate and relevant indicators to a harmonized EU health data system and to assist the EC in setting priorities for information and knowledge on major and rare diseases.\(^9\) On 30 November 2009, the Rare Disease Taskforce was replaced by the establishment of the European Union Committee of Experts on Rare Diseases (EUCERD; see below).\(^9\)

On 11 November 2008, the European Commission published its ‘Communication on Rare Diseases: Europe’s Challenges’. The Communication focused on the improvement of recognition and visibility of rare diseases, support for policies on rare diseases of member states for a coherent overall strategy and the development of cooperation, coordination and regulation for rare diseases at EU level.\(^10\) This communication led to the adoption of the European Council Recommendation on an Action in the Field of rare diseases in June 2009.\(^10\)

The Recommendation notably focuses on national plans and strategies of Member States which should be adopted by 2013 to improve recognition of rare diseases, encourage research in the field of rare diseases and forging links between Member States through the creation of European reference networks in order to share knowledge and expertise.\(^10\)

The EUCERD was established to aid the European Commission with the preparation and implementation of Community activities in the field of rare diseases.\(^10\) The EUCERD consists of 51 members, which includes one representative from each government agency or ministry responsible for rare diseases of each Member state, four representatives from patient organisations, four representatives from the pharmaceutical industry, nine representatives from ongoing and/or past Community projects financed by the health programmes (including three members of the pilot European Reference Networks on rare diseases), six representatives of ongoing and/or past rare diseases project financed by the Community
Framework Programmes for Research and Technical Development, and one representative of the European Centre for Diseases Prevention and Control.  

The EUCERD publishes an annual overview of initiatives and incentives in the area of rare diseases by the EU and individual Member states. This also includes an overview of DG Research and Innovation’s fifth, sixth and seventh Framework Programmes for research, technological development and demonstration activities related to rare diseases.

### 6.1.3 Community Actions in the Field of Health (Health programmes)

‘Programmes of Community Action in the Field of Health’ are the main instrument the European Commission uses to implement the EU Health Strategy. Rare diseases have been included in these Community Actions for over a decade. In 1999 a ‘Programme of Community Action on Rare Diseases’ within the framework for action in the field of public health was established (1999-2003) with a budget of 6.5 million euro. This programme aimed for the development of a European network on rare diseases, information, education and updating on professionals knowledge, creation of transnational collaborations and networks and creation of systems improving collection, analysis and dissemination of knowledge in the field of rare diseases. In this community action programme 24 projects were funded.

The following ‘Programme of Community Action in the Field of Health’ (2003-2008) with a total budget of 312 million euro, was based on three general objectives: improving information and knowledge, enhancing a rapid reaction in a coordinated fashion to health threats and promoting health and preventing disease. The programme replaced a series of eight EU programmes that each focused on individual health issues, such as cancer, AIDS and other communicable diseases, rare diseases and drug abuse. Rare diseases were mentioned under the second objective.

The ‘Second Programme of Community Action in the Field of Public Health’ (2008-2013) with a total budget of 3 215 million euro was based on three general objectives: improving citizens’ health security, promoting health, which involves reducing inequalities in this area and generating and disseminating health information and knowledge. Rare diseases were mentioned under the second objective. For the years 2008-2011, a total of 21 434 895 euro was awarded to rare disease-related projects. An additional €4.5 million was planned for 2012.

Recently, an overview of eight projects was published, which receive(d) funding from the EU through Community Actions in the Field of Health, and which illustrate some of the actions that have been undertaken at Community level to reduce the burden of rare diseases.

Of course, the aforementioned projects are examples of many projects and other initiatives that have been funded by the EC.
Table 6.19.2: Projects to illustrate some of the actions that have been undertaken at Community level to reduce the burden of rare diseases

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Eurordis</td>
<td>Patient advocacy and support organisation that promotes cooperation between rare disease patient organisations across the EU, with a myriad of educational and advisory activities that promote the empowerment of patients.</td>
</tr>
<tr>
<td>Orphanet</td>
<td>Improves the recognition and visibility of rare diseases by offering patients and health care professionals up-to-date, relevant information on rare diseases, orphan drugs and expert services.</td>
</tr>
<tr>
<td>ECORN-CF Care-NMD</td>
<td>The creation of European Reference Networks, linking centres of expertise and professionals in different countries, is essential to both share knowledge and to identify where patients should go when expertise is unavailable in their home country. ECORN-CF and CARE-NMD are two projects where treatment recommendations and a consensus in clinical care are being promoted for cystic fibrosis and Duchenne muscular dystrophy respectively.</td>
</tr>
<tr>
<td>Eurocat RareCare</td>
<td>Many EU-funded projects encourage more research into rare diseases. Understanding the scale and scope of rare diseases is often an issue, particularly when clinicians and patients struggle to find the right diagnosis and treatment. Two projects EUROCAT and RARECARE present detailed European epidemiological data on congenital anomalies and rare cancers respectively.</td>
</tr>
<tr>
<td>Eurocat European Newborn Screening</td>
<td>Projects like EUROCAT promote wide-ranging networks of expert knowledge to better understand rare diseases and support evidence-based action. For example, the review of European Newborn Screening practices will guide future European policy, enabling the appropriate diagnostic and preventive measures to be put into action in all Member States.</td>
</tr>
</tbody>
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6.1.4 Framework programmes

At European level, research on rare diseases has been addressed as one of the priority areas in the health field under the EU Framework Programmes for Research and Technological Development since the early 1990’s.106

The aforementioned EUCERD annual overview of initiatives and incentives in the area of rare diseases by the EU and individual member states also includes an overview of DG Research and Innovation’s fifth, sixth and seventh Framework Programmes for research, technological development and demonstration activities related to rare diseases.

During the fifth framework programme for research support was provided for multinational research into rare diseases. Forty seven projects were funded for about €64 million in total.57
An example of a project funded by FP5 is the EuroBioBank with 1.2 million euro for 36 months that stimulated the infrastructure of rare diseases. This bank is the first of biological banks in Europe providing human biological material (DNA, tissues, cells) for research on rare diseases on a large scale. The consortium was originally composed of 16 partners from eight European countries, 12 academic or private banks, 2 computer services companies (software designer and developer), one biotechnology company and EURORDIS who initiated the project. A total of approximately 65 000 DNA samples and 15 000 tissue samples are available via the 12 banks of the consortium.

During the Sixth Framework Programme for Research (FP6 2002-2006), one of the seven thematic areas focused on “Life sciences genomics and biotechnology for health”. FP6 saw a significant increase in the funding for rare disease projects; around £230 million for a total of 59 projects, one of which was an ERA-Net Project. The outcomes of this funding was mobilization of research to tackle fragmentation of research, better coordination at EU level and the fostering of dialogue with stakeholders.

The Seventh Framework programme (FP7 2007-2013) encompasses four main programmes: “Cooperation”, “Idea”, “People” and “Capacities”. The Cooperation programme supports collaborative research and is subdivided into 10 themes, including the ‘Health Theme’, under which most research on rare diseases falls. The emphasis of rare disease research is on studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. Special attention has been given to communicating research outcomes and engaging in dialogue with civil society, in particular with patient groups.

The European Commission has already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. Between the period of 2007-2010, 50 research projects on rare diseases have been supported. Approximately 17 of these projects are fundamental research, whilst eight projects cover preclinical and clinical development of orphan drugs. One of the projects funded by FP7 has been the Orphan Platform, which was a three year (2008-2011) project, aimed to help develop a platform for researchers in rare diseases to quickly and efficiently set up multidisciplinary teams and exchange information within EU Member States. It also produced an inventory of publicly funded projects in the field of rare diseases and orphan drugs.

6.1.5 Actions at Member State level

Apart from Programmes of Community Actions for Public Health and Framework Programmes at EU level, individual EU Member states have also addressed the burden of rare diseases in the last decade. As mentioned above, the EUCERD provides an extensive annual overview of initiatives and incentives in the area of rare diseases by the EU and individual Member States. Initiatives and incentives by individual member states cover extensive categories in relation to rare diseases.

Examples are: national plans or strategies for rare diseases and related actions; presence of centres of expertise; neonatal screening policy; National alliances of patient organisations and patient representation and research activities.

Although Member States fund rare disease research, specific rare disease research programmes at Member State level are limited. Moreover, some countries have dedicated centres of expertise for certain rare diseases, others have not.
However, as mentioned above, the 27 EU Member States have committed to adopt National Plans/Strategies for responding to rare diseases before the end of 2013\textsuperscript{101} in their European Council Recommendation on an Action in the Field of rare diseases, adopted in June 2009.\textsuperscript{101} The collaborative EU-level Recommendation document aims to guide actions in rare diseases within the Member States’ health and social systems. To facilitate the process of developing complementary and effective plans, the European Commission funded the European Project for Rare Disease National Plan Development (EUROPLAN) between 2008-2011 and extended to 2015.\textsuperscript{109} The EU member states are currently in the process of adopting and implementing national plans and strategies for responding to rare diseases. The plans should ensure that rare disease patients have access to high quality care and if possible access to effective orphan drugs.\textsuperscript{109,110,111} France was the first EU country to adopt, at the end of 2004, a national rare disease plan (see Box 6.19.1).

Plans can be reviewed on the EUROPLAN website (www.europlanproject.eu), which shows the current stage of development of national plans or strategies for rare diseases in the EU.

**Box 6.19.1: National rare disease plan in France**

France’s first initiative in rare diseases was the creation of a French programme in 2002 with specific funds from public and charities. For the creation and/or development of 59 networks for rare diseases and promotion of 27 multidisciplinary research projects a budget of 7.9 million euro was made available for 2002 and 2003. Next to this funding programme, the development of partnerships and infrastructure was started, e.g. a partnership with the French Mouse Clinical Institute to generate mouse models for rare diseases. The programme formed the basis for the adoption of a national rare disease plan at the end of 2004. France was the first EU country to define a specific strategy on how to deal with the problems associated with rare diseases at a national level. The second national plan was elaborated by the Ministry of Health. The second plan was launched on 28th February 2011 with a budget of €180 million. Before the end of 2013 a third plan will be discussed.

### 6.2 The Rest of the World

#### 6.2.1 United States of America (USA)

Within the USA, rare disease research has been given a stimulus with the Rare Diseases Acts of 2001-2002.\textsuperscript{112} The Rare Diseases Act of 2001 (S. 1379; S.R. 107-239) started two initiatives and was split later into two separate acts, the Rare Diseases Act of 2002 (H.R. 4013) and the Rare Diseases Orphan Product Act of 2002 (H.R. 4014), that were passed in November 2002.\textsuperscript{113,114} Emphasis was given in 2003 to the building of rare disease regional centres of excellence for clinical research into, training in, and demonstration of diagnostic, preventive, control, and treatment methods for rare diseases.\textsuperscript{114}

The Rare Diseases Act of 2002 (H.R. 4013, Public Law 107-280) has provided the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) a statutory authorisation to increase the national investment in the development of diagnostics and treatments for
patients with rare disorders. Since then several programmes have been initiated in the area of rare diseases:

a) Undiagnosed Diseases Program
As mentioned above some patients wait years for a definitive diagnosis. Using a unique combination of scientific and medical expertise and resources at the NIH, the Undiagnosed Diseases Program aims to provide answers to patients with mysterious conditions that have long eluded diagnosis. Moreover, a second objective is to advance medical knowledge about rare and common diseases.

b) Therapeutics for Rare and Neglected Diseases program (TRND)
TRND is a collaborative drug discovery and development program with a $24 million budget per fiscal year since 2009.

c) Rare disease Bench-to-Bedside Awards
As part of the Bedside-to-Bench (B2B) Program in 2012 seven B2B awards were granted for rare disease-specific projects. The aim of the B2B Program is to fund projects that focus on translation of basic scientific findings into therapeutic interventions for patients and to increase understanding of important disease processes. A B2B award provides up to $135 000 a year for two years.

d) Rare Diseases Clinical Research Network (RDCRN)
The Rare Diseases Act of 2002 also resulted in the establishment of rare disease regional centres of excellence for clinical research into, training in, and demonstration of diagnostic, preventive, control, and treatment methods for rare diseases. On October 2009, the NIH funded rare diseases clinical research consortia and one Data Management Coordinating Center. This cooperative program should facilitate many advances including the identification of biomarkers for disease risk, disease severity/activity, and clinical outcome and encourage development of new approaches to prevention, diagnosis, and treatment of many rare diseases beyond those being studied. The easy and free availability of data from the Data and Technology Coordinating Center should also spawn many new research ideas and subsequent applications to NIH Institutes and Centers.

The Office of Orphan Products Development (OOPD) at the U.S. Food & Drug Administration (FDA) has been dedicated to promoting the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions since it was created in 1982. OOPD interacts with the medical and research communities, professional organizations, academia, and the pharmaceutical industry, as well as rare disease groups. The OOPD is the administrative body for the Orphan Products Development Grant Program. The objective of this OOPD grant program is to fund trials that will result in new products or data to be used in the treatment of rare diseases. The products studied can be drugs, biologics, medical devices, or medical foods, but in practice they are primarily

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3 Spinocerebellar ataxias, urea cycle disorders, primary immune deficiency, porphyria, mitochondrial disease, salivary gland carcinomas, nervous system channelopathies, dystonia, mucocilary clearance, nephrotic syndrome, graft versus host diseases, vasculitis, hereditary causes of nephrolithiasis and kidney failure, Angelman syndrome/Rett syndrome/Prader-Willi syndrome, autonomic rare disease, inherited neuropathies, sterol and isoprenoid diseases, lysosomal disease and brain vascular malformation
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drugs and biologics. The current annual budget for funding grants is now approximately $14 million due to the Rare Disease Orphan Product Development Act of 2002 (H.R. 4014). Clinical trials are awarded grants from US$ 100,000 to US$ 200,000 per year in direct costs for up to three years. This program has led to increased research and development of orphan products at academic institutions and other responsible organizations: public, private, non-profit, or for-profit. The grants (over 500 until now) have enabled scientists to develop the preliminary scientific data necessary to prove that a new treatment warrants commercial development and FDA approval. These grants helped to bring more than 45 products to market approval.

The USA has a treatment IND protocol that can applied to rare disease patients. The IND treatment protocol is used when no satisfactory alternative treatment exists, for a life-threatening and debilitating illnesses, the patient can access promising therapeutic agents which have not yet been market approved. The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The only countries in Europe with similar protocols are France and Italy.

Additionally, the U.S. Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) and accompanying PDUFA Reauthorization Performance Goals and Procedures for Fiscal Years 2013 through 2017 provide for several regulatory science initiatives to enhance the development of drugs for rare diseases by improving existing processes and creating new ones. Center for Drug Evaluation and Research (CDER) will increase staffing for the Rare Disease Program by five and create a new rare disease liaison position in the Center for Biologics Evaluation and Research (CBER) Office of the Center Director. FDASIA further aims to address development challenges for drugs targeting rare diseases by instructing FDA to specifically consider the issues arising under the Accelerated Approval and Fast Track provisions for such products including the chance to qualify for classification as a “breakthrough therapy” (FDASIA §901, §902). When approving a rare disease drug under its new Accelerated Approval authorities, FDA is asked to consider broader information in the assessment of benefit/risk, such as the severity and rarity of the condition and the lack of alternative treatments. FDA will seek input from external rare disease experts and patient advocates by holding public meetings and developing a list of such experts to serve as advisors for rare disease drug development (FDASIA §903). Finally, the law offers priority review vouchers as an incentive for novel pediatric rare disease drugs (§908) and amends the humanitarian device exemption (FDASIA §613).

6.2.2 Japan

Japan has the oldest programme for rare disease research and care in the world. The Specified Rare Diseases Treatment Research Programme was established in Japan in 1972 with the support of the Ministry of Health, Labour and Welfare. One-hundred and thirty diseases have so far been the subject of research programmes and research grants form government sources. In 2010, the government expanded the budget to 10 billion yen.

6.2.3 China

Due to China’s large population there is a large pool of rare disease patients. This has allowed China to conduct large genome studies on rare disease. Recently Beijing Genome
Institute has launched the “1000 Mendelian Disorder Projects”, These research studies have greatly developed China’s research interests in studies to better understand the genetic background of rare diseases. So far the Mendelian Disorders Project has initiated genetic studies covering more than 150 diseases. There are no national network for rare diseases in China and diagnosis of rare diseases is only possible in large cities within the country. This means that much of the needs of China’s rare disease patients are not met. Additionally there is very limited development of drugs for rare diseases in China because no policies for incentives have been adopted. China included the development of orphan drugs in a national programme for innovative new drugs in 2010. A definition of rare disease was proposed by a group of medical experts in 2010 and an initial list of 23 rare diseases has been proposed.

6.3 International collaboration

In the field of rare disease research maximising scarce resources and coordinating research efforts is key. In order to address this issue the International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 at the initiative of the European Commission and the United States National Institutes of Health with the aim of fostering international collaboration in rare diseases research. The goal is to pool resources and work beyond borders in order to get a better understanding of rare diseases and find adequate treatments. Apart from the EC and the NIH, private as well as public organisations from EU Member States, Australia, Canada and the USA have joined the IRDiRC as funding body. The IRDiRC teams up researchers and organisations investing in rare diseases research. It has two main objectives: to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by 2020. Recently, the European Commission announced that it will provide €144 million of new funding for 26 research projects. Over 300 participants from 29 countries in Europe and beyond will be brought together in the selected projects, including teams from leading academic institutions, smaller businesses and patients’ groups. The 26 new projects cover an array of rare diseases including cardiovascular, metabolic and immunological disorders.

6.3.1 Funding by patients

The role of rare disease patients in rare disease research and orphan drug development is enormous and at all stages of the drug innovation cycle. Rare disease patients or their parents initiate research, provide the necessary funding, provide input to research agendas, own patents, initiate product development programs, maintain registries and biobanks, and even start their own companies. The National Organization for Rare Disorders (NORD), a non-profit, voluntary health agency exists to serve rare-disease patients and their families in the USA. The Research Grant Program of NORD provides seed money in small grants to academic scientists studying new treatments or diagnostics for rare diseases. The clinical researchers supported by NORD’s research grants provide preliminary data indicating that a treatment (drug, device, or medical food) may be safe and effective when used for a larger number of patients. Researchers can then use the preliminary data to apply for larger multi-year government grants or to attract a commercial sponsor.

With regard to orphan drug development, apart from well-established sources of funding like governmental grants and venture capital, patient-initiated research foundations can also represent an important source of funding. Funding of translational research as well as (pre-)
clinical proof of concept studies is not only directed to academic institutes, but also academic spin-offs/start-up companies and more mature SMEs. The French Muscular Dystrophy Association (AFM) serves as a good example in this respect with the creation of Genethon, a company that focuses on gene therapy. In 2012 the new innovative cystic fibrosis product Kalydeco™ was approved by the FDA. Although the product has been developed by Vertex Pharmaceuticals, its development was to a large extent funded by the Cystic Fibrosis Foundation. In France, Lysogene, a company founded by a parent of a child with Sanfilippo syndrome type IIIA (mucopolysaccharidosis IIIA), is working on a gene therapy product. Another example is the AKU society that is collaborating with academia and industry to study the potential clinical effect nitisinone, a product approved for tyrosinemia type I (orfadin), may have in alkaptonuria. This has been made possible by EU funding, and it was the patients’ group that was the driving force behind setting up the consortium, design the programme and applying for the funding. These are only a few examples.

7. What Are the Gaps Between Current Research and Potential Research Issues which Could Make a Difference, Are Affordable and Could Be Carried out in a) five years or b) in the longer term?

In the last decade considerable attention has been paid worldwide to stimulate the research, development and bringing to the market of orphan medicinal products by the pharmaceutical industry. In the USA and the EU over 400 and 70 OMPs have been approved as therapy for a rare disease. Many orphan medicinal products are innovative, biotechnological products that have been the start for several small biotech-companies. Apart from treatments coming available, the introduction of various (research) programmes and networks has advanced understanding and diagnosis of several rare diseases as well.

However, despite the growing number of approved orphan drugs and enhanced rare disease understanding in the last decade, many gaps remain related to the development of treatments and care for patients with a rare disease. Being a complex and heterogeneous mosaic of an estimated 5000-8000 conditions, it has become clear that the (research) need can differ considerably between (groups of) rare diseases:

Lack of disease understanding: need for fundamental research into disease process

For many rare diseases basic knowledge, like diagnosis, cause of the disease, pathophysiology, natural course of the disease and epidemiological data that would allow for development of preventive, diagnostic and/or therapeutic approaches is limited or worse missing. This significantly hampers the ability to both diagnose and treat these diseases. For those diseases funding of fundamental biomedical research is necessary. Genomic research will result in the recognition of more rare genetic diseases or subclasses. Proteomic research will result in more insight in protein function and structure of proteins that are deficient or are accumulated in rare diseases. Ongoing fundamental research into the disease process will result in more targets for pharmaceutical intervention or healthcare innovation for rare diseases. While only a small number of pharmaceutical companies are engaged in investing
in fundamental research in rare diseases, public research is of utmost importance, and will help increase public-private partnerships in view of new therapy development.

To support the development of scientific knowledge ultimately useful to patients, investments in fundamental research in disease process need to go hand in hand with investments in dedicated rare disease infrastructure and pan-European or even global networks. Where needed, these networks will also provide effective medical education and opportunities to train health professionals on rare diseases.

The availability of a rare disease classification system is equally important to make rare diseases more visible in health information systems. This will be an important step to help generate reliable epidemiological data. Such a system will constitute a useful basis for further research into the natural history and etiology of rare diseases, allows monitoring safety and clinical effectiveness of therapies and measuring quality of care. Several systems are currently considered suitable for coding rare diseases diagnosis: International Classification of Diseases-11 (ICD11; currently in Beta phase), the Orphanet classification, OMIM and SNOMED CT. Each system has its advantages and disadvantages, and important questions remain unanswered with regard to funding and maintenance of such a system.

Translation of disease understanding into product development or healthcare innovation is hampered.

As aforementioned, the majority of designated and approved orphan drugs in the USA and EU were intended for treatment of rare diseases in the field of oncology followed by metabolism. The latter indicates that translation of rare disease research into an orphan drug development is not equally spread across disease classes, which was confirmed by Heemstra et al.

Consequently, a lack of treatment remains for many rare disorders, which is a clear pharmacological gap. Although the development of orphan drugs is in essence the primary responsibility of the pharmaceutical industry, public funding could focus on proof of concept studies and act as a catalyst to translate rare disease research into orphan drug development. In the EU at Member State level, translational research programmes are limited.

Apart from treatment, disease understanding may also translate into healthcare innovations. Beyond focusing on finding a cure, research should also focus on providing easy and accurate diagnosis and on prevention strategies. As has been shown above for PKU, some interventions to avoid organ damages require early diagnosis (e.g. newborn screening) to be effective and decrease the reliance on curative interventions.

Most OMP designations are for pharmaceuticals intended to treat rare diseases. The OMP designation system covers diagnosis and prevention in its criteria as well, but is less adequate to stimulate diagnosis and prevention. Products and techniques for diagnosis most of the time do not require a marketing authorisation and the technical development follow a different cycle than drugs. Prevention can be understood in two different ways either prevention of disease occurrence or prevention of symptoms or relapse of symptoms. Prevention of disease occurrence relies on adapted behaviors and in case of rare genetic disorders also on proper genetic counselling. Prevention of symptoms and organ damage are
related to the timing of a treatment or intervention hence the importance of early diagnosis. It is therefore not unusual that nearly all the approved orphan drugs in the EU are intended for treatment of rare diseases and not for diagnosis or prevention. However, diagnosis and prevention strategies represent important tools in reducing the burden of rare diseases. Specific incentives for researchers and industry to tackle these two dimensions of care more prominently are welcome.

For some rare diseases translation of research into product development or healthcare innovation has taken place, but further development is hampered.

### 7.1 Clinical trials

A key issue with rare diseases is that they present with fundamentally different challenges than more common diseases, like asthma or diabetes. This is most apparent during the clinical development stage where rarity significantly complicate the developers task: too small a number of patients geographically dispersed throughout the world, logistics, ethics (e.g. use of placebo), lack of validated biomarkers and surrogate end-points, poor diagnostics, limited clinical expertise and expert centres, high administrative requirements which vary from country to country, and from clinical trial site to clinical trial site.

Clinical trial-funding programmes (e.g. orphan products grant program) remain essential for orphan drug development for rare diseases that receive less attention from the pharmaceutical industry (e.g. less prevalent).

Critical for marketing authorization and reimbursement is the acceptance of the evidence generated with methods adapted to small to very small population. Further development and/or optimization of alternative methodologies in clinical investigation in small populations to meet the criteria for marketing authorization and to provide information for pricing or reimbursement decisions are desirable (See Chapter and Background paper 8.3). Regulatory authorities, which have gained extensive experience with small-sized clinical trials, can represent an added-value in this respect.

Similar to fundamental research, large multidisciplinary networks should be funded to stimulate collaboration between all interested parties bringing together medical experts, reference centers, and patients’ groups for rare diseases. This infrastructure is necessary for developing clinical guidelines that can help the physcians in the diagnosis and therapeutic decision tree, reinforcing the performance of clinical trials and subsequent monitoring of the new products through (public-private) registries.

### 7.2 Innovative therapies

The first clinical proof of concept study of alipogene tiparvovec (Glybera®), the first gene therapy product approved in the EU, was partially funded through a translational research programme of the Netherlands Organisation for Health Research and Development (ZonMw). Alipogene tiparvovec is an excellent example of a whole new generation of more targeted therapies, like stem cell therapies, gene therapies or therapeutic gene modulations (exon skipping, antisense drugs, RNA interference). To allow these targeted therapies for smaller
patient groups to become more common practice in the future, it is critical to continue funding the research and development of these highly innovative therapies through specific budgets or public-private partnership (PPP) programs.

7.3 Innovative drug delivery methods

Innovative drug delivery methods are discussed in depth in Chapter 7.4 of this report. The use of (other) delivery methods for existing orphan drugs would be of significant benefit for patients with rare diseases. These methods entail an improved pharmacokinetic profile of existing orphan drugs, and consequently an improved efficacy, safety profile or contribution to patient care. For rare disease patients the ability to measure the added value these innovative drug delivery methods bring to patients and/or the health care system will be critical to justify the additional developments costs for industry. The reason why innovative drug delivery systems remain underused in the area of orphan drugs is unclear. Increased patient involvement will certainly increase demand for more convenient administration schemes and devices. Some examples of innovative drug delivery systems are:

1) Alternatives for intravenous administration
   For example enzyme replacement therapy for several lysosomal disorders (Gaucher disease, Fabry disease) is given intravenously, either in the hospital or at home. The frequency of these infusions, that take about two hours per infusion, may vary widely from three times a week to once a month. It would be a great advantage for these patients when the supplemented enzyme could be given in another way, e.g. via a tablet or capsule.

2) Controlled delivery systems
   Another example of patients with a rare disease that could benefit from an improved delivery method are Addison patients. Many Addison patients are substituted with corticosteroids due to an adrenal cortical insufficiency. The capsules are taken three times a day. However, it would be much better for the patients to mimic the natural situation as much as possible by a controlled delivery of the corticosteroids in the body.

3) Site-specific drug delivery
   Another important issue is the delivery of drugs across the blood brain barrier. Many patients with rare diseases have neurological symptoms. It would be a major breakthrough for the treatment of these diseases when large molecules could be targeted across the blood brain barrier.

7.4 Drug repurposing

Another opportunity for research in pharmacological intervention for rare diseases is the use of molecules that are running out of patent protection. Some of these molecules could be further developed for new indications e.g. rare disorder. This is known as drug repurposing. The advantage is that these molecules have obtained a marketing approval or have gone through considerable clinical testing for another indication. Consequently, preclinical and safety data is available with sometimes clinical experience (off label use) in the targeted indication. The new molecule will still need to be developed for registration in the new indication to define dose, safety, efficacy and even if relevant how to optimize delivery. In this case also clinical readiness is critical to expedite development (diagnosis, epidemiology, natural history, endpoints to study, rare disease patients ready for enrollement). Review of
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the EU Register of Orphan Medicinal Products indicates that several companies exist that have built their business model around the concept of drug repurposing. Regulatory requirements and market access arrangements for new use of out of patent molecules may however still present some significant hurdles.

Although slightly different the screening of available public and private drug libraries for potential leads for rare diseases may also hold great promise in the discovery and subsequent development of novel therapies for specific rare diseases.

8. CONCLUSION

In the area of rare diseases there are many opportunities for the EU to build on the successful programmes, projects and networks that have been supported since 2000. The most important ones that should continue to be supported are:

- Networks of excellence that focus on research infrastructure (e.g. registries) as well as provision of disease-related information at EU level and beyond (guidelines, diagnosis, patient experience)
- Initiatives that focus on rare disease classification
- Fundamental research into the disease process to increase rare disease understanding
- Incentives for development of therapeutics (e.g. clinical trial-funding programmes)
- Assessment methods adapted to small and very small patient populations (e.g. marketing authorisation and reimbursement).

In addition, more support is needed for:

- Translational research to increase translation of disease understanding into drug development or healthcare innovation (e.g. NIH bench to bed grants)
- Innovative diagnostic methods of rare diseases to enable early intervention
- Research, infrastructure as well as implementing guidelines for medical and psychosocial care for rare diseases. This would be especially beneficial for those patients for whom underlying treatment is not yet available.
- Incentives for development of preventive strategies and validated diagnostic techniques
- Incentives to leverage existing knowledge and optimize the use of existing drugs (innovative drug delivery systems and drug repurposing).
- Giving easy access to available healthcare (diagnostic, medical, pharmacological or other types of care) to patients regardless of where they live.

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### Annex

**Annex 6.19.1: Orphan drug policies in different countries**

<table>
<thead>
<tr>
<th>Program established</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
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<tr>
<th>Prevalence criterion for rare disease</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 200,000 patients in USA (&lt;7.5: 10&lt;sup&gt;5&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Life-threatening or chronically debilitating disorder that affects less than 5:10&lt;sup&gt;5&lt;/sup&gt; in EU</td>
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<tr>
<th>Requirements for designation</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
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<tbody>
<tr>
<td>Rare disease or R&amp;D costs cannot be recovered in seven years</td>
<td>Rare and serious disease; no other treatment available, must be a high health care priority</td>
<td>Drugs with major indications for the prevention, diagnosis and treatment of rare diseases</td>
<td>Rare disease or product is not commercially viable</td>
<td>Rare disease, or product unlikely to be developed without incentives or new product will be of significant benefit</td>
<td></td>
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<table>
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<tr>
<th>Products eligible for orphan designation</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
<td>Drugs, biologicals and medical devices</td>
<td>Drugs and biological and special nutrient foods</td>
<td>Drugs, vaccines or in vivo diagnostic agents</td>
<td>Drugs and biologicals (including vaccines and in vivo diagnostics)</td>
<td></td>
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<tr>
<th>Market exclusivity</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
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<tr>
<td>Seven years; prevents same product being approved for the same indication unless clinical superiority is shown</td>
<td>Re-examination period extended from four to ten years</td>
<td>Ten years. During this period, no applications for registration and market approval of pharmaceuticals of the same kind will be approved</td>
<td>None; second product with the same active ingredient will not be designated unless clinical superiority is shown</td>
<td>Ten years; can be reduced to six if orphan criteria no longer met</td>
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<thead>
<tr>
<th>Other benefits</th>
<th>United States</th>
<th>Japan</th>
<th>Taiwan</th>
<th>Australia</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory fee waivers, 50% tax credit on clinical research after designation; grants for clinical research (pharma and academia eligible); protocol assistance; faster review if indication warrants; research grants for medical devices and medical food.</td>
<td>Application fee reduced (?); grants for clinical and non-clinical studies (only pharma eligible) up to 50% of yearly R&amp;D costs available up to three years; 6% tax reductions for (pre) clinical research; protocol assistance on request; faster review if indication warrants.</td>
<td>Patients’ ailments are now included in National Health Insurance coverage for major diseases and injuries and whose co-payment can be waived.</td>
<td>Regulatory fee waivers; no grants, no tax credits, protocol assistance on request; priority review</td>
<td>Regulatory fees can be reduced or waived, access to centralized procedure, protocol assistance. Individual Member States have to implement measures to stimulate the development of orphan medicinal products (Article 9 of Regulation)</td>
<td></td>
</tr>
</tbody>
</table>

Source: reference 28,50,119-123