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ORPHAN DRUGS

UNDERSTANDING THE RARE DISEASE MARKET AND ITS DYNAMICS

ELIZABETH HERNBERG-STÅHL AND MIROSLAV RELJANOVIĆ

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Orphan drugs

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E. Hernberg-Ståhl and M. Reljanović

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About the authors

Elizabeth Hernberg-Ståhl, MSc, is the founder of Late Phase Solutions Europe AB, an independent consultancy based in Sweden, which focuses on providing strategic and operational guidance on late phase drug development as well as guidance on processes and activities related to orphan drug development and market access.

The author has more than 30 years of experience in the international biotech and pharmaceutical industry (20 of which were in the orphan drugs arena). During her 10 years at TKT/Shire Human Genetic Therapies, Elizabeth was responsible for developing and establishing the Global Outcome Survey Department, which manages global patient registries. Elizabeth was also a member of the Shire HGT European Management Team and the Global Medical Affairs Leadership Team. Before joining Shire, Elizabeth held a similar position for 8 years at Pharmacia/Pfizer where she established and managed a global patient registry KIMS on the rare condition adult growth hormone deficiency (GHD) and the outcome of growth hormone treatment. Elizabeth has published numerous papers and is a frequent speaker at congresses on topics related to orphan rare diseases.

Miroslav Reljanović, MD, MSc, is a board-certified neurologist. Whilst practising as a physician in a large WHO Collaborating Centre in Zagreb, he was the clinical investigator in numerous Phase II and III studies in the field

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of neurology and a consultant to various pharmaceutical companies.

In 1997, Miro founded Ergomed contract research organization (CRO) and he introduced the novel Study Site Coordination model as an intrinsic part of the conduct of clinical studies. This model became a landmark of the Ergomed approach to clinical research, which is paramount to provide high quality trial data in very demanding areas like oncology, neurology and orphan diseases, including rare cancers. Miro has also successfully introduced the first European innovative co-development business model and he has completed several transactions with European and North American listed biopharmaceutical companies.

Together with co-founder Elliot Brown, MB, MRCGP, FFPM, a well-known international expert in drug safety, Miro started PrimeVigilance in 2008, which soon became a leading specialist vendor of contracted pharmacovigilance services to the pharmaceutical industry.

Through a strategic partnership with Elizabeth, Miro established a specific division at Ergomed, focusing on providing assistance and support to biotechnology and drug industries, clinicians and researchers to facilitate the development of candidate drugs for rare diseases in this challenging field.

For further information, please see: *www.ergomed-cro.com/rare-diseases*

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Introduction

Patients suffering from rare diseases were not well served until the US Orphan Drug Act (ODA) of 1983 was put in place to stimulate and motivate the worldwide pharmaceutical and biotechnology industry to develop treatments for this patient group. The main rationale and cornerstone of this regulation from its inception was to put the rare disease patient at the centre of all activities and to ensure that they have the same access to medical treatments as patients with any other disease.

> *Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including . . . medical care. . . .*
>
> (Universal Declaration of Human Rights, United Nations 1948)

Before these regulations and incentives for the industry were put in place only a handful of drugs were approved for patients with rare diseases. A drug under development may be granted orphan drug status under this legislation if it meets certain criteria in a formal application process. In order to be eligible for orphan drug designation (ODD), the intended target indication must satisfy specific orphan disease criteria such as rarity. The indication will also be evaluated for medical plausibility and to determine

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whether the new drug has the potential to provide significant benefit to the affected patients. If the drug is assigned orphan drug status, further support is available during clinical development through incentives provided in the legislation, together with a potential reduction in the manufacturer's financial risk as a result of the defined period of market exclusivity following marketing authorisation.

Orphan drug legislation has been in place since 1983 in the USA and since 2000 in Europe. It is an important and successful legal framework that has motivated the pharmaceutical industry to invest in the development of new treatments for formerly neglected diseases.

Indeed, the success of the orphan drug legislation (together with the incentives that are associated with it) is underlined by the steady increase in the number of designations for orphan designation seen in Europe: 107 designations were granted in 2011, 148 in 2012 and more than 150 are expected in 2013. In-line with this trend, in 2012, 19 applications for marketing authorisation concerned designated orphan medicines, compared with 14 in 2011.

Table 0.1 gives a more complete picture.

A similar picture is seen in the USA, where there were 2730 designations for orphan drugs, and 421 approvals up to 31 December 2012.

More information on orphan drug designation and approvals in the USA can be found at: *www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*

However, despite the large number of orphan drug designations, from looking at the data above and from the data in Table 0.1, it can also be seen that while many drugs have received regulatory approval, many of the designated products failed during the course of development, and never reached the market. As with non-orphan drugs, there is no

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Table 0.1 Overview for orphan medicinal product designation procedure since 2000

Year	Applications submitted	Applications discussed in reporting year	Positive COMP opinions	Applications withdrawn	Final negative COMP opinions	EC designations	Orphan medicinal products authorised
2013	16	27	20 (74%)	6 (22%)	1 (4%)	13	0
2012	197	192	139 (72%)	52 (27%)	1 (1%)	148	12
2011	166	158	111 (70%)	45 (29%)	2 (1%)	107	5
2010	174	176	123 (70%)	51 (29%)	2 (1%)	128	4
2009	164	136	113 (83%)	23 (17%)	0[2] (0%)	106	9
2008	119	118	86 (73%)	31 (26%)	1 (1%)	73	6
2007	125	117	97 (83%)	19 (16%)	1 (1%)	98	13
2006	104	103	81 (79%)	20 (19%)	2 (2%)	80	9
2005	118	118	88 (75%)	30 (25%)	0 (0%)	88	4
2004	108	101	75 (74%)	22 (22%)	4 (4%)	73	6
2003	87	96	54 (56%)	41 (43%)	1 (1%)	55	5
2002	80	75	43 (57%)	30 (40%)	2[3] (3%)	49	4
2001	83	90	62[4] (70%)	27 (29%)	1 (1%)	64	3
2000	72	32	26 (81%)	6 (19%)	0 (0%)	14	0
Total	**1613**	**1539**	**1118 (73%)**	**403 (26%)**	**18 (1%)**	**1096**	**80**

[2] Negative opinion adopted in 2009 was revised and finalised in 2010, therefore it is not included in 2009 listing.
[3] Following a quality assurance exercise it was identified that this figure needed correction.
Source: Taken from EMA/COMP/63660/2013

information available for most of these orphan drugs as to why they failed early in development. Despite numerous approved new medicines for rare diseases, most of the patients affected by the 5000 to 8000 rare diseases still remain without cure or treatment. There is ongoing huge, unmet medical need to improve the lives of these patients with fatal and disabling conditions.

Most companies dedicated to development of orphan drugs are small and middle sized companies. However, in the last few years several big pharmaceutical companies have entered the field. This gives hope that a new wave of orphan drugs may become available over the next years, as it is possible that at least some of the lack of progress in orphan dug development might have been caused by limited resources or financial shortcomings.

Unfortunately there are many misconceptions around the orphan drug legislation. It has been seen as a shortcut to faster market access for drugs with a high price and long-lasting exclusivity. Some of the misinterpretations of the current orphan drug legislation are:

- a higher probability of regulatory approval;
- smaller trial sizes result in lower overall development costs;
- less clinical development time on average;
- less regulatory review time on average;
- once approved for marketing the orphan drug will be highly profitable;
- the orphan drug market is generally less price sensitive.

These misunderstandings may increase the risk of an unwillingness to reimburse such medicines by public payers and a negative impact on the access to new innovative drugs for the affected patients.

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This book attempts to provide some help in understanding the original goal of orphan drug incentives, why they are important for the patient and what problems a pharmaceutical manufacturer may encounter to bring them to market. It is a first introduction to the world of rare diseases and orphan drugs. The book is intended to be a companion for the journey from the application of an orphan drug designation to a reimbursed market-approved drug.

After reading the text, the reader will better understand:

- what an orphan designation means around the world, as there is no one single international definition;
- what the main steps involved in orphan drug development are and where to find more in-depth information;
- what a rare disease is beyond prevalence figures, and what broad spectrum of diseases are summarised under the definition;
- what role patient advocacy groups, as a major stakeholder, or patients have in the direct support of orphan drug development or in driving policy questions related to improvements in the life of patients with rare diseases;
- what research and policy initiatives have been initiated by the US Congress and the European Union (EU) commission or other political decision-makers;
- what rare disease initiatives are dedicated to the specific condition;
- what operational and regulatory hurdles are encountered in designing robust clinical trials for orphan drugs to ensure the same standard of safety and efficacy as drugs for common diseases;
- why orphan medicines, despite the same Market Authorization Approval as non-orphan drugs, may not be

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automatically available for patients and reimbursed by public health systems.

What is unique within the world of rare diseases is the strong partnership between all of those involved in the rare disease community. There are a number of stakeholders that are specific for rare diseases, such as Orphanet, the National Organization for Rare Disorders (NORD) and the European Rare Diseases Organisation (EURORDIS). These stakeholders, such as patient organisations, take an active role in the influencing of general policy on behalf of the rare disease patients. Both NORD and EURORDIS played a very important role in the introduction of the orphan drug legislation and they are still driving many important health policy issues.

There are many research initiatives on rare diseases that are dedicated to rare diseases that still lack treatment, and support research into new therapies. Research into rare diseases may result in models that allow a better understanding of mechanisms that are applicable to more common diseases.

The book will not be able to convey all the passion that is involved in this field; however, it provides an insight into the numerous activities and various partners involved. A flavour of this is seen in the event entitled Rare Disease Day. This event happens on the last Friday in February.

The Sixth International Day took place on 27 February 2013 and was coordinated by EURORDIS and organised with rare disease national alliances in 24 European countries. On and around this day, hundreds of patient organisations from more than 60 countries and regions worldwide conducted awareness-raising activities converging around the slogan 'Rare Disorders Without Borders'.

This involved activities being scheduled to take place across Europe, Russia, China, Japan, the USA and Canada, Australia and New Zealand.

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As with the Rare Disease Day, this book is aimed to target a broad audience with different backgrounds and interests, but driven by the same passion to make a change to the lives of rare disease patients. The seven chapters can be read consecutively or individually. A comprehensive reference list is placed at the end of each chapter, which may help the more advanced reader/expert in the field to find additional information.

The reader's contributions to future editions of this book are highly appreciated. Please forward any ideas, comments or corrections in writing to the authors.

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1

Orphan drugs and orphan drug legislation

With additional contributions by Chris Wilson

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Abstract: This chapter explains the definition of orphan drugs and provides some background to the related regulations that have emerged in the USA and other regions including the EU, Japan and Australia. The development of orphan drug regulations over the last 30 years in the USA and during the last 10 years in Europe will be briefly reviewed and the current orphan legislation and incentives will be discussed. The procedure to apply for an orphan drug designation in both regions and the regulatory process to achieve market authorisation, including protocol assistance and scientific opinion, and conditional approvals, including post-approval commitments, will be described.

Key words: orphan drug, definition, legislation, incentives, EU, USA, regulatory process.

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1.1 The history of orphan drug legislation

1.1.1 Why was orphan drug legislation introduced?

Estimates vary, but it is thought that between 5000–8000 rare diseases have been identified worldwide. There are different estimates as to how many patients there are that suffer from these rare diseases, but it is thought that there are at least 55 million patients with a rare disease in the EU and the USA, although some of the diseases are extremely rare with only a few hundred patients affected. Examples of these are Hutchinson-Guilford Progeria Syndrome, often referred to as progeria, which causes a person to age prematurely, Creutzfeldt-Jakob disease, which is a fatal brain disease, and lymphangioleiomyomatosis, which is a rare but fatal lung disease.

One in 17 people will be affected by a rare disease at some point in their life, and this translates into approximately 246 000 people per disease throughout the EU's 27 Member States (*www.raredisease.org.uk/*).

It is estimated that today in the EU, rare diseases affect 6–8% of the population – between 27 and 36 million people.

If all rare diseases are considered as a single group, it can be seen that they are not rare at all and in fact many patients are affected by a rare disease. Indeed, rare diseases are becoming less rare due to our increasing understanding of pathophysiology, resulting in the separation of broad disease categories into smaller and more well-defined disease entities. About 250 new rare diseases are described each year (Wästfelt et al. 2006).

Clearly, all patients should have the right to treatment, irrespective of frequency of disease, and indeed, in The

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Universal Declaration of Human Rights, adopted in 1948, it states, in Article 25.1:

> *Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including . . . medical care . . . .*

The ethical implications of this are clear – governments have the responsibility to intervene in the drugs market to ensure the provision of life-saving treatments to even small patient populations.

However, before orphan drug legislation was introduced, rare diseases were not a priority for the pharmaceutical and biotech industry, as it was not considered profitable to develop drugs for small patient cohorts. To bring a new pharmaceutical drug to the market is, and was, both time-consuming and very costly. The development of a new drug often includes several years of basic research to find a substance for a promising drug candidate. This is followed by studies on animals and clinical trials on patients to provide data that must be reviewed and assessed before a drug is approved. To make a complicated procedure even more complicated, very often there are no in vivo animal models for rare diseases.

Before orphan drug legislation was introduced in the USA (in 1983), people with rare diseases were denied access to effective medication because manufacturers could rarely make a profit marketing drugs to such a small group. This resulted in only a few drugs being approved for orphan indications including calcitrol for the treatment of hypocalcaemia in dialysis patients in 1978, metoclopramide for the treatment of gastroparesis in 1979, and alprostadil for treating neonates with congenital heart defects before surgery in 1981. However, during the first year after

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introducing the new legislation, there were 15 requests for designation, of which 10 were granted.

It is interesting to note that the driving force behind the implementation of the orphan drug legislation, both in the USA and later on in Europe, was not the pharmaceutical industry, but rather patient organisations.

In the early 1980s several rare disease patient organisations in the USA worked diligently to highlight the lack of focus from industry in developing treatments for these rare diseases. By utilising different public relation approaches and working closely with, for example, journalists, attention in the USA was finally brought to bear on this disease area.

Following the increase in public awareness, the US congress and senate realised the huge unmet medical need for patients with rare disease and the orphan drug legislation was born.

The terms 'orphan drugs' and 'orphan diseases' come from the Greek word '*orphanos*', which means a child who has lost one or both parents or an adult who has lost a child. So the reason for naming drugs for rare diseases as orphan drugs, is that they are 'very much like children who have no parents and they require special effort' (US Representative Henry A. Waxman (D-CA)), and because in the past no drug company wanted to 'adopt' them (Bohrer and Prince 1999).

The orphan drug legislation that followed was the ODA, which was signed into law by President Ronald Reagan in 1983. The objective of the ODA was to encourage the pharmaceutical industry and to stimulate it to overcome the various hurdles in developing orphan drugs aimed at treating rare orphan diseases. This encouragement was through economic incentives and special assistance during the FDA drug approval process. This is discussed in more detail below.

Once the ODA had become law in the USA, other countries followed this example; legislation was introduced in Singapore in the 1991 'Medicine (Orphan Drug) Exemption

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order', in Japan in 1993 with a revision of the Pharmaceutical Affairs Law, in Australia in 1997 (establishing their orphan drugs policy), in 1998 in Korea (which established the Korean Orphan Drug Centre) and in Taiwan in 2000 with the Rare Diseases and Orphan Drugs Act.

In Europe at this time, there were a limited number of national orphan drug initiatives, but at the pan-European level, one of the first steps in addressing the question of orphan drugs was issued in the European Council Resolution of 20 December 1995 (95/C 350/03), in which a number of aspects were to be considered:

1. The definition of an 'orphan' drug.
2. The definition of a 'rare' disease, having regard to its prevalence.
3. The criteria for obtaining 'orphan' drug status in Europe, establishing conditions for a drug's inclusion or exclusion, in the light of any changes in the conditions on the basis of which they were classified.
4. Measures using regulatory provisions (including intellectual property aspects) and financial incentives to promote research, development, marketing authorisation and distribution of orphan drugs.
5. Examination of the health impact of a European policy on orphan drugs in the Member States and its economic impact for European industry.

The Orphan Drug legislation (Regulation (EC) 141/2000 on Orphan Medicinal Products (OMP) came into force in Europe in 2000, and as in the USA, only a limited number of drugs (15) were available for the treatment of rare diseases before that time (e.g. Cerezyme, Caelyx and MabThera). This was not due to a lack of interest in Europe, but more as a result of the fact that the EU first had to be established in

order to provide initiatives at the European level. The European Parliament and Council adopted the regulation on Orphan Medicinal Products in December 1999, and in April 2000 the regulation was adopted by the European Commission.

1.2 Legislation and the definition of orphan disease in different countries

As already indicated, in addition to the USA and the EU, other countries such as Japan, Australia, Taiwan, South Korea, Hong Kong and Singapore have either adopted US Food and Drug Administration (FDA) / European Medicines Agency (EMA) regulations or they are developing their own guidelines to support activities related to orphan products.

India and New Zealand are in the process of establishing similar regulatory processes, but in a number of countries, for example Brazil, Chile, Mexico and Colombia, there is no specific orphan drug legislation, because it is felt that patients have access to essential medicines used in the treatment of rare diseases through existing mechanisms such as the Emergency Drug Release Programme.

1.2.1 Orphan drug legislation

USA

ODA was introduced in 1983 and contained incentives to industry, including 50% tax credits on research expenditure. These incentives were initially to cover the cost of developing and marketing a treatment for any disease or condition that occurred so infrequently that there was no reasonable

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expectation the costs would be covered by the sales generated within the USA.

Companies could also receive technical assistance with their clinical development plan, and access to the fast track procedures at the FDA to speed up the marketing authorisation approval during this process. Once approved for marketing, the orphan drug was granted 7 years of market exclusivity. This will be further discussed in Chapter 5.

To be eligible for consideration under the ODA, the product had to be in the process of being studied in man and in an active phase of marketing authorisation approval. Over the years the ODA has undergone several amendments and changes to the eligibility criteria. For example, more than one sponsor may receive an orphan drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for the designation (Seoane-Vazquez et al. 2008).

In addition, during the 7-year market orphan exclusivity, the FDA cannot approve a new drug application (NDA) or a generic drug application for the same active ingredient in the same rare disease indication, although the FDA could approve a second application for the same active ingredient for a different disease indication.

A second drug containing the same active ingredient can be approved for the same orphan indication if the sponsor can show it is clinically superior to the original orphan drug that is already on the market. This can be achieved by either showing that the second drug is more effective, safer or otherwise makes a major contribution to patient care.

It should be noted that although legislation states that fewer than 200 000 individuals should be affected in the USA for the disease to be considered orphan, a drug can be considered orphan even if more than 200 000 patients are

affected if the cost of development cannot be covered by sales generated in the USA.

Since its introduction, the ODA orphan definition has been extended to also include products other than drugs: biologics, medical devices and medical foods (parental nutrition).

Additional changes have been suggested such as the FDA should be more flexible when considering the approval of orphan drugs and acknowledge the problems in clinical trial design given the low number of patients that may be available. Other proposed changes relate to the fact that often data on the natural history of the disease itself may be lacking, or that the use of biomarkers to measure surrogate study endpoints should be more widely accepted. A suggestion has also been made that the threshold for orphan disease should now be updated to reflect the fact that the US population has increased by 35% since 1983.

However, the most recent changes to the 1992 orphan drug regulations (21 CFR 316) proposed at the end of 2011 by the FDA are intended to clarify certain regulatory provisions and make minor improvements to address issues that have arisen since the regulations have been in place.

The proposals are designed to provide clarification in the follow 13 areas:

- demonstration of an appropriate 'orphan subset' of persons with a particular disease or condition that otherwise affects 200 000 or more persons in the USA for the purpose of designating a drug for use in that subset;
- eligibility for orphan drug designation of a drug that is otherwise the same drug for the same orphan indication as a previously approved drug;
- eligibility for multiple orphan drug exclusive approvals when a designated orphan drug is separately approved for use in different subsets of the rare disease or condition;

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- requirement for demonstrating clinical superiority for the purpose of orphan drug exclusive approval;
- requirement for submitting the name of the drug in an orphan drug designation request;
- required drug description and scientific rationale in a designation request;
- required information in a designation request relating to the sponsor's interest in the drug;
- timing of a request for orphan drug designation;
- responding to a deficiency letter from the FDA on an orphan drug designation request;
- FDA publication of information regarding designated orphan drugs;
- FDA recognition of orphan drug exclusive approval;
- miscellaneous terminology changes;
- an address change.

For more details on the above, the reader is referred to published information on the website of the FDA Office of Orphan Products Development: *www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm*

www.gpo.gov/fdsys/pkg/FR-2011-10-19/pdf/2011-27037.pdf

For information on the Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law on 9 July 2012 and the Prescription Drug User Fee Act (PDUFA) V and their impact on orphan drug legislation, the reader is referred to Chapter 5.

European Union

In Europe only drugs for human use can be designated as an orphan medicinal product; as a result, veterinary medicines,

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medical devices, nutritional supplements or dietary products are not eligible.

The sponsor of a potential orphan medicinal product must apply to the Committee of Orphan Medicinal Products at the EMA (the EU regulatory agency for the evaluation of medicinal products) for an orphan designation. If it can be demonstrated by the Sponsor that the potential orphan drug is indicated for the prevention, treatment or diagnosis of a life-threatening or chronically debilitating disease with a maximum prevalence of 5 patients in 10 000 inhabitants (with data to support this claim), and that it will be of significant benefit over other available treatments for those affected by the condition, an orphan designation can be awarded.

The manufacturers of drugs with an orphan drug designation are, as in the USA, entitled to several incentives, of which a market exclusivity of 10 years upon authorisation is viewed as the most important. Other incentives are direct access to the centralised procedure for European marketing authorisation (which results in a single licence that permits marketing in all EU countries), fee reductions for regulatory procedures, scientific advice (this is advice given to a company on the appropriate tests and studies required to develop a medicine) and protocol assistance (a special form of scientific advice available for companies developing medicines for orphan or rare diseases) during the product development process.

EMA fee reductions for designated orphan medicinal products are shown in Table 1.1.

In contrast to the USA, tax incentives are not provided in the EU at community level.

For more details see the EMA website: *www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce&jsenabled=true*

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Table 1.1 EMA fee reductions for designated orphan medicinal products

Procedure or service	Fee reduction applicable to	Percentage fee reduction
Protocol assistance, initial and follow-up requests	SME sponsors for all assistance	100
	Non-SME sponsors for non-paediatric-related assistance*	40
	Non-SME sponsors for paediatric-related assistance*	100
Pre-authorisation inspection	All sponsors	100
Initial marketing authorisation application	SME Sponsor	100
Post-authorisation applications and annual fee, in the first year from granting of a marketing authorisation	SME sponsors	100

* Paediatric-related protocol assistance is restricted to development of an orphan medicinal product for the paediatric population, where the advice requested does not include the adult population.

SME small and medium sized enterprises.

Source: Taken from EMA/663496/2012, 16 December 2011 (Fee reductions for designated orphan medicinal products).

Japan

To promote the development of orphan drugs, the Japanese Department of Health and Welfare initially issued a Pharmaceutical Affairs Notification in June 1985. This early Notification acknowledged some of the difficulties in developing a drug for a disease with very few patients, as it included a clause providing some flexibility on the acceptance of non-Japanese clinical data.

This initial initiative was followed on 1 October 1993 by the Japanese government revising the Pharmaceutical Affairs Law and introducing special provisions relating to the research and development of orphan drugs.

A drug can obtain orphan status in Japan if the targeted disease is incurable and there are no possible alternative treatments, or the efficacy and expected safety must be significantly better in comparison with other available drugs. In addition, the number of affected patients must be fewer than 50 000 in Japan.

Under the legislation, administrative and financial incentives are available. The financial incentives provide access to Governmental funds to cover a proportion of expenditure associated with research and development.

A grant can be applied for from the National Institute of Biomedical Innovation (NIBIO). The company can be asked to repay the amount to the NIBIO based on the profit from sales after approval. This will not exceed the amount of the grant. In addition, there is a 12% tax reduction for eligible research and development expenses. This is given for companies that have received the grant from the NIBIO.

The incentives also cover access to a Fast Track Marketing Authorization procedure. The Japanese Organization for Pharmaceutical Safety and Research provides consultations on development protocols as well as some advice on the application. Once approved, the product has the re-examination period extended up to 10 years for a drug and up to 7 years for a medical device. During this period the same drug cannot be approved for the same indication.

For more details see the website of the Japanese Ministry of Health, Labour and Welfare: *www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html*

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Australia

The Australian orphan drugs policy was set up in 1997. The Australian Orphan Drug programme uses information from the FDA as part of their evaluation process. The prevalence of a disease should be fewer than 2000 patients in the Australian population, which corresponds to 1.2 in 10 000. In addition, the drug should not be commercially available in the indicated population. Unlike in the USA or Japan, research and development is not supported by grants or tax incentives; however, there are no filing fees for an orphan drug.

For more details see the website of the Therapeutic Goods Administration (TGA): *www.tga.gov.au/industry/pm-orphan-drugs.htm*

Singapore

Singapore's Medicine (Orphan Drug Exemption) order, introduced in 1991, defines a rare disease as a life-threatening and severely debilitating illness affecting fewer than 20 000 persons, and an orphan drug as a medicinal product that:

(a) has been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute available for the treatment of any rare disease;

(b) has not been granted a product licence under the Act; and

(c) has been approved by the competent health authorities either of the country of origin or of any other country where the orphan drug has been used.

Although there are no incentives given in the exemption, the licensing authority may permit any person to import or supply any orphan drug without a product licence if the drug is to be used by a doctor or dentist who has prescribed the

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drug for the treatment of a patient under his care. However, as soon as an application for a product licence for the drug has been approved by the licensing authority, the product loses its orphan status.

For more details see the website of the Health Sciences Authority: *www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/legislation.html*

Hong Kong

The Department of Health (DOH) is responsible for health legislation and policy in Hong Kong, and it is the Pharmaceutical Service within the DOH that is responsible for drug registration and drug import/export control.

An orphan drug applicant may register their drug under the New Chemical Entity (NCE) registration process, which was established for new, life-saving drugs. In this case, the application will be processed immediately and reviewed by the Hong Kong DOH Pharmaceutical Licensing Committee. This Committee only meets four times a year, so applicants should make an effort to submit their application several weeks prior to a Committee meeting to reduce processing time.

A second registration process is available for those applicants that cannot meet the NCE application requirements. The second option, registering under the 'normal' registration process, takes 6–9 months to complete.

For more details see the website of the DOH:
www.dh.gov.hk/eindex.html

Taiwan

In Taiwan, the Rare Disease Control and Orphan Drug Act became law in 2000 and addressed the following aspects of orphan drug legislation: the acquisition of orphan drugs, R&D, manufacturing orphan drugs, diagnosis and treatment

of rare diseases, prevention, acknowledgement of rare diseases, cooperation with international rare disease organisations, and the subsidised supply of specific pharmaceuticals and special nutrients.

Pharmaceuticals approved as orphan drugs are granted a 10-year marketing exclusivity period in Taiwan and during this time the Department of Health will not accept registration applications for any similar drugs.

In addition, some conditions officially classified as 'rare diseases' under the Rare Disease Prevention and Medicine Law in Taiwan, entitle patients to full financial reimbursement for medication.

For more details see the website of the Department of Health: *www.bhp.doh.gov.tw/bhpnet/English/ClassShow.aspx?No=200803260026*

Korea

Although there is currently no rare disease / orphan drug legislation in place in Korea, nor a national plan or strategy for rare diseases, a number of actions have been initiated by the Ministry of Health and Welfare. This includes the establishment of a non-profit organisation Orphan Drug Centre in 1999, supported by the Korean Food and Drug Administration (KFDA; renamed the Ministry of Food and Drug Safety in March 2013), which supplies medications for rare diseases. The KFDA has also defined, in an official notice, rare diseases as diseases affecting fewer than 20 000 persons in Korea without appropriate treatment and substitution treatment modalities. The Ministry of Health has also established a Genetic and Rare Disease Centre in 2004, which deals with the subsidies for medical expenses related to rare diseases, and organises national reference centres (established in 2006) and research in the field of

genetic and rare diseases. The Rare Disease Centre also acts as an information centre, and from 2006 has provided a helpline service for patients. In 2008, a research grant for rare diseases was launched by the Ministry of Health for the period 1 April 2008 to 31 March 2012, to fund basic research and a clinical research network with around US$5.5 million.

For more details see the website of the Ministry of Food and Drug Safety: (*www.kfda.go.kr/eng/index.do*).

Argentina

Argentina initiated regulation on orphan drugs through the National Administration for Food, Drugs and Technology's (ANMAT) Disposition 7266/2008 of 16 December 2008, for those products manufactured in national manufacturing laboratories. According to this regulation an orphan drug is defined as a drug with a high therapeutic interest and scientific viability that is not available due to different reasons or circumstances to treat or ameliorate the health problems of a patient.

Recently Argentina promulgated a law to promote public access to medicines, vaccines and medical devices and enhance scientific and technological development of healthcare products via public laboratories (Ley 26.688). Law 26.688, published in the *Boletín Oficial de la República Argentina* on 2 August 2011, involves creating a framework for improving the availability of healthcare products and advancing scientific research through federal-, provincial- and municipal-level laboratories and laboratories run by state universities. The main topics of the act include the definition of a rare disease – Argentina is adopting the same prevalence of less than 1/2000 that is used in the EU. Furthermore, the health system must now provide specific

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assistance to patients and their caregivers. In addition, public and private social security schemes are obliged to provide specific support. A central multidisciplinary committee is to be created in order to coordinate these actions and will include patient organisations. A national registry of patients will be elaborated and a neonatal screening programme will be considered, along with educational, social and support activities that are all mentioned in the law. All of these activities need governance, and different levels of government must be coordinated before the effects of this dramatic development can be felt, but stakeholders believe that a significant first step has been taken.

For more information, please scroll down to see 'National & international policy developments' on the following website: *www.orpha.net/actor/EuropaNews/2011/110803.html*

Peru

Peru has also issued its first national law concerning patients with rare diseases. Law 29698 promotes treatments for rare conditions and includes a national strategy covering diagnostics, surveillance, prevention, care and rehabilitation. While Peru has not developed a precise definition of orphan disease based on prevalence, this legislation is considered a big step forward for rare disease patients in Peru.

The text of the Peruvian Law (in Spanish) can be accessed at: *www.orpha.net/actor/EuropaNews/2011/doc/PeruLaw.pdf*

Canada

Health Canada is currently developing a framework for the designation, authorisation and monitoring of orphan drugs

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that will provide a significant benefit to Canadians with rare diseases and motivate research and innovation in Canada. A key focus of this new approach will be in regard to international information-sharing and collaboration for the development and regulation of orphan drugs. Once authorised, drugs will continue to be closely monitored for effectiveness and safety while in use.

In a press release, BIOTECanada, the country's national industry association representing biotechnology companies, observed that with the '. . . creation of a regulatory pathway for rare disease medicines, the Government will be providing patients with greater access to innovative treatments addressing their unique medical needs' (*www.biotech.ca/en/policy-matters/health-bio/rare.aspx*).

Definition of orphan disease in different countries

There is currently no global international harmonisation between countries or regions regarding the cut-off level for a disease to be considered orphan. The prevalence figures (number of people living with a disease at a given moment) vary between 1 in 10 000 and 10 in 10 000.

Some examples of the cut-off level for prevalence figures for a rare disease to be considered an orphan disease are as follows:

- In the USA, the disease has to affect fewer than 200 000 patients, or less than 7.5 in 10 000.
- Japan has a cut-off level of fewer than 50 000, or fewer than 4 patients in 10 000.
- Australia fewer than 2000 patients, or fewer than 1.1 in 10 000.
- EU fewer than 5 in 10 000.
- Canada, based on information currently available (2013), not more than 5 per 10 000 inhabitants.

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It is therefore easy to see how critical it is for a prospective sponsor to have defendable data to support a request for orphan status, and in particular when it comes to subsets of disease. The term 'salami slicing' has been used extensively in the last couple of years. This refers to a company requesting an orphan designation by dividing a disease into smaller subpopulations in order to meet the orphan drug prevalence. This is something not only the agency but also payers are concerned about (see Chapter 7).

An acceptable example of this practice is when a disease subset is clearly demarcated, has its own specific pharmacological mechanism, and the proposed orphan drug has no effect in the rest of the population. In the USA, an example of a medically plausible subpopulation could be a toxic drug that only the most severely ill patients would use due to the toxic effect overweighing the drug's benefits (e.g. stage IV cancer). In the EU, an example could be where a subset of a disease has already been granted an Orphan designation. This is the case for ascorbic acid for Charcat-Maire-Tooth Disease where it received orphan designation for those patients expressing the CMT1A-F variant gene.

Examples of unacceptable subpopulations would include different stages or severity of a condition, where the proposed orphan product might also have value in the rest of the condition. So subsets based on a post-hoc analysis of a study where the product was intended to work in the whole group would fall into this category.

Finally it is interesting to note that the evaluation of whether a population can or cannot be regarded as an orphan population is likely to become more difficult and complex in the future, as the development of targeted therapies and personalised medicine leads to an increasing segmentation of patients into subpopulations.

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1.3 Current state of the art: number of designations and approvals

1.3.1 State of the art orphan designations and approvals in the USA

Seoane-Vazquez et al. 2008 conducted a review of designations and approvals in the USA from 1983–2007.

They found that the majority of sponsors who had received an orphan designation had in total a low number of orphan designations, 509 (62.8%) sponsors had only one orphan designation, and cancer was the primary focus for research equating to approximately one quarter of all applications (25.5%). Most of the orphan designation approvals were concentrated among a relatively small group of sponsors, 155 (19.1%), and these sponsors had received 43.2% of the total designations. A total of 8.3% of the sponsors that had received 5 or more orphan designations accounted for 60.2% of the approvals in the USA.

As of 31 December 2012, from a search of the ODA database, 2730 products have been designated orphan drugs by the FDA and more than 400 medicines for orphan diseases have received marketing authorisation approval since the inception of the ODA, compared to fewer than 10 in the 1970s. Approximately 20% (460) of these drugs are in late stage development, meaning in clinical trials or under review by the FDA.

Eleven of the 30 new drugs (37%) approved in 2011 by the FDA were for rare medical conditions (genetic disorders such as cystic fibrosis, with 67 drugs in development, neurological disorders such as multiple sclerosis and muscular dystrophy, with 37 medicines in development). This is the highest percentage on record since the FDA began offering incentives to develop such therapies about 30 years ago.

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Additionally, nearly half of the 30 drugs were cleared under the FDA's 'fast track' programme reserved for drugs that fill an unmet medical need. Among the innovative treatments approved in the past year were the first new drug for lupus in 50 years and the first new drug for Hodgkin's lymphoma in 30 years.

And so it is easy to see, with more than 2500 drugs having received orphan drug designation in the USA, including 170 in 2011 (Figure 1.1), the impact of the legislation (a total of 2730 designations and 421 approved drugs, figures current as of 31 December 2012 – FDA website). Similarly, more than 1000 orphan drug applications with mainly successful designations and a trend for steady increase have been filed in the EU during the last 10 years (Figure 1.2). The largest group of orphan medicines for which the Committee for Orphan Medicinal Products (COMP) has adopted a positive opinion up until 2010 were treatments for oncology (45%), followed by treatments for central nervous system (CNS)/musculoskeletal disorders, metabolic

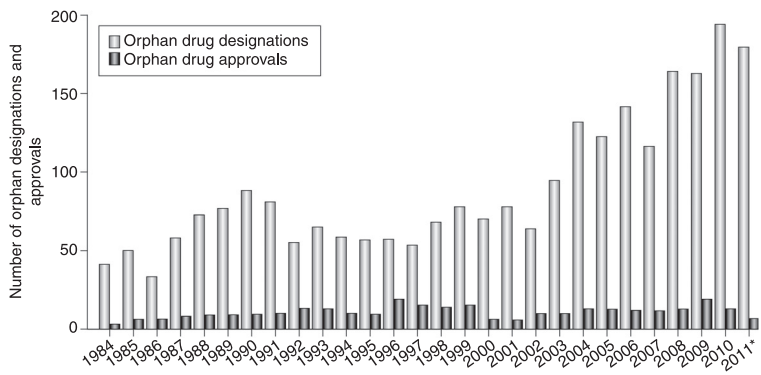

Figure 1.1 **Overview of orphan drug designations and approvals in the US from 1984 to 2011**

Source: Reprinted with permission from Melnikova (2012)

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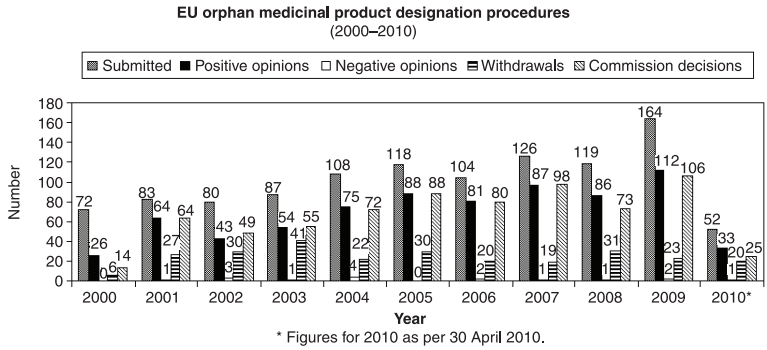

Figure 1.2 **Status of orphan-designation applications in the EU from 2000 to 2010**

Source: EMA (2010, p. 4)

disorders, immunology, cardiovascular/respiratory disorders (approximately 10% each). Approximately one half of the medicines that have received a positive opinion on orphan designation are for conditions that affect both children and adults, a further 8% for conditions that affect exclusively children, with the remaining 42% for medical conditions affecting adults only (European Medicines Agency EMA/279601/2010).

A new US Government study has identified that a niche area where a growing number of drugs are now coming to market is in the development of orphan drugs to help treat rare diseases in children (Thorat et al. 2012). In this study, officials at the FDA found that between 2000 and 2009, there were more than three dozen orphan drug approvals for rare disorders affecting children and teenagers. In the first half of the decade 2000–2009, just 10 out of 57 orphan drug approvals were for paediatric conditions, while in the latter half of this period it had risen to 28 out of 91.

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1.3.2 State of the art orphan designations and approvals in the EU

Although the EU orphan drug legislation was introduced later than in the USA, over the initial 10 years more than 850 positive opinions for orphan medicinal product designation were given to 1235 applications that were reviewed.

This initial success is further underlined by the steady increase seen in the number of orphan designations (see Table 0.1): 107 designations were granted in 2011, 148 in 2012, and more than 150 are expected in 2013. In-line with this trend, in 2012, 19 applications for marketing authorisation concerned designated orphan medicines, compared with 14 in 2011.

In 2012, a number of substances that received orphan designation were intended for the treatment of diseases for which no treatment existed and no orphan designation had previously been granted, such as Prader-Willi syndrome and hereditary inclusion body myopathy (HIBM).

The distribution of the prevalence of conditions for which the designation has been adopted shows that the most frequently designated conditions have been those that affect fewer than 1 in 10 000 patients (a total of 52% of all designations). In addition, 51% of the orphan medicinal products that have obtained market authorisation in the EU are for the treatment of diseases affecting fewer than 1 in 10 000 patients. The number of applications has increased steadily each year during the first decade of the regulation with a total of 174 applications received in 2010.

Table 1.2 provides a breakdown of COMP's opinions on orphan drug designations by therapeutic area, where it can be clearly seen that the majority of positive opinions are in the field of oncology.

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Table 1.2 EU COMP opinions on orphan drug designations by therapeutic area

Therapeutic area	Orphan drug designation (%)	Market authorization (%)
Oncology	45.2	35.5
Musculoskeletal and nervous system	12.4	3.2
Other	10.3	24.2
Immunology	9.7	4.8
Metabolism	9.7	24.2
Cardiovascular and respiratory	9.4	8.1
Anti-infectious	3.3	0

Source: Orphan Medicines in Numbers EMA/279601/2010.

Sixty-three designated products had received marketing authorisation by the end of 2010 and, unsurprisingly given the large number of positive opinions in this therapeutic area, the largest group were for oncology treatments. The average time span between orphan designation and authorisation is 2.8 years, indicating that designated products were at an advanced developmental stage.

To access the most up-to-date information, the European Commission maintains a register of orphan medicinal products, broken down into 'active', 'withdrawn or suspended' and 'refused' products, and this information can be downloaded from:

http://ec.europa.eu/health/documents/community-register/html/index_en.htm

Most orphan medicinal product applications in Europe have originated from small companies. Heemstra et al. 2011 estimate that approximately 85% of the orphan designation applications originate from small and medium sized enterprises (SMEs). This term is legally defined in the

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EU Commission Recommendation 2003/361, but the main factors determining whether a company is classified as an SME are the number of employees (i.e. fewer than 250 employees for a medium sized company) and either turnover or balance sheet total (i.e. a ceiling of ≤ €50 million for a medium sized company).

For these companies the EU regulation has provided an important opportunity to demonstrate the potential of new technology platforms and drug products, and it is starting to play an important role in stimulating innovation in the area of life sciences.

Indeed, within Europe there has been a steady increase in the number of advanced therapy medicinal products (i.e. fusion proteins, monoclonal antibodies, cell and gene therapy products, tissue engineered products, oligonucleotides) obtaining orphan designation, and these drugs now represent 7% of all designated products. Overall, approximately 30% of all orphan drug designations are classified as innovative (*www.eurordis.org/content/celebrating-10-years-orphan-drug-regulation-europe*).

1.4 Players on the market

With 5000–8000 rare diseases and only a few of them for which treatment exists, there remains a high level of unmet medical need. Significant opportunities therefore exist, and pharmaceutical and biotechnology companies continue to invest in research and development.

Traditionally the orphan drug arena has tended to be the focus of smaller companies and biotech companies. Indeed, half of the biotechnology products approved in the USA in the period 1982–2002 were designated orphan drugs, and this has been a major factor in stimulating the growth of the

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US biotechnology industry. It is interesting to note that several of the world's largest, USA-based, biotech companies had an orphan drug as their first product.

Many small companies work very closely with patient advocacy groups and have a strong and clear vision of wanting to make a difference for patients and their families. This includes an important strategy of continuing to build disease communities, forming partnerships with all involved stakeholders, and being prepared for a long-term commitment.

There is now an increased interest from many large companies to enter the orphan drug field, including large pharmaceutical companies. Companies such as Pfizer and GlaxoSmithKline (GSK) now devote parts of their organisation to focus on rare diseases and orphan drugs. In February 2010, GSK created a dedicated unit for orphan drug development, and in July 2010, Pfizer implemented a new division for new treatments for rare diseases.

The recent interest of big pharmaceutical manufacturers in the rare disease area is explained by some to be due to lack of blockbusters in their pipeline, although they claim that they select their research programmes based on unmet medical needs and not market size. Orphan diseases are also an interesting research topic as the diseases often have a phenotype or a genotype that is easily discernible and which could be applicable to a larger patient population. Medical breakthroughs in the orphan arena therefore have the potential to be applied to broader patient populations.

An example of this is fragile X disease, which is associated with mental retardation that occurs almost exclusively in boys. Scientists are now beginning to understand the genetic determinants of the disease and are asking whether associated treatments could have relevance in the treatment of Alzheimer's disease.

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The most important predictor for a company to obtain authorisation for an orphan drug is related to the previous experience of the company. Companies that have successfully brought an orphan drug to the market increase their odds of obtaining market authorisation for consecutive orphan drugs more than 17-fold (Heemstra et al. 2008).

Apart from previous experience, are there any other factors that might impact on the successful development of an orphan drug? For example, does market exclusivity hinder the development of Follow-on Orphan Medicinal Products in Europe? This is something Brabers et al. (2011) have looked into in more detail. They examined whether the market exclusivity incentive of the European Orphan Medicinal Product Regulation resulted in a market monopoly or the absence of another OMP for the same rare disorder. The impact of various market-, product- and disease-related characteristics on follow-on OMP development in the EU was determined by comparing rare disorders with an approved OMP and at least one follow-on OMP (n = 26), with rare disorders with an approved OMP and no follow-on OMP (n = 18).

The likelihood of a rare disorder with an approved OMP to obtain at least one follow-on OMP development was strongly associated with disease prevalence, turnover of the first OMP, disease class, disease-specific scientific output and age of onset. Out of a total of 120 follow-on OMPs only one follow-on OMP could be identified for which development was discontinued upon approval of the first OMP for the same rare disorder. Only a substantial level of discontinuation of follow-on OMP development would have indicated the existence of a market monopoly. Moreover, sponsors that continued development of a follow-on OMP predominantly assumed that their product had an improved efficacy compared to the first approved OMP.

This study provides evidence that absence of follow-on OMP development is a matter of time or market size, rather than that the market exclusivity incentive of the European Orphan Medicinal Product Regulation creates a market monopoly.

1.5 Contribution made by orphan drug legislation

Has the orphan drug act/legislation helped patients or industry or both? From the information already presented, it can clearly be seen that following the publication of the ODA in the USA, and similar legislation in other countries, more orphan drugs have been developed and approved, although not all of them have received access to patients in all countries. This is an issue that will be discussed more in Chapter 7.

From the patient perspective, the legislation has made a huge difference, as in the example of cystic fibrosis patients – before treatment was available their life expectancy was rather short, rarely past the age of 10 years. Today they can survive to an age of approximately 30 to 50 years.

The Orphan Drug Act and legislation in the EU has not only contributed to new drugs for a patient cohort that for a long period has had no attention from researchers and the pharmaceutical industry, it has also contributed to society in a broader respect; for example, the EU legislation has not only helped established companies to invest resources in the field of rare diseases, but also in the creation of new companies. Employment in all departments of companies working in the field of orphan disease increased 158% between 2000 and 2008. OMP related research and development expenditures in the EU increased by 209% during this period (Mestre-Ferrandiz et al. 2010).

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The implementation of the orphan drug legislation has also had an impact on healthcare systems in terms of wider benefit to patient families and increases in the medical expertise on rare diseases, as well as the implementation of research networks and infrastructure, thus facilitating knowledge exchange (Mestre-Ferrandiz et al. 2010). Further information is provided in Chapters 3 and 4.

In a study commissioned by industry (the European Biopharmaceutical Enterprises (EBE) and the regional bio-industry association (EuropaBio)) to assess the impact of the EU OMP Regulation since its adoption, the authors state that the Regulation has been 'one of the most successful EU healthcare policies overall'.

The study found that research and development focused on finding new treatments for rare diseases represents an increasingly significant proportion of the biopharmaceutical industry's total research and development investment. Moreover, for nearly all of the companies that have been created to focus exclusively on researching and developing orphan medicinal products since the Regulation was adopted, all their research and development activities and staff are located in the EU.

The study states that incentives provided in the legislation have 'greatly fostered innovation and entry into market of therapies addressing hitherto unmet medical needs'. The authors also note that the Regulation has not only provided support to companies investing in such treatments but, importantly, has helped to establish new companies in Europe focused on researching new treatments for rare diseases. So, from industry's perspective, orphan drug legislation has achieved at least some of its objectives, by continuing to provide funds for research and grant programmes, and this funding has increased both in the USA and in the EU (see also Chapter 5).

The legislation has opened up the possibility for small biotech companies to get the chance to bring drugs to the market in many cases based on a specific technique; for example, Biomarin with their proprietary enzyme technology, and Amicus with their work on small molecule pharmacological 'chaperones'.

From the regulatory assessors' perspective, certainly in the USA, several new jobs have been established both within the administration at the FDA and also in the National Institutes of Health (NIH) Office of Rare Diseases.

1.6 Procedure: orphan drug designation and marketing authorisation approval

1.6.1 US application procedures

The FDA website has detailed instructions on how to apply for an orphan designation. The content and format of a request for orphan drug designation can also be found in section 316.20 of the Code of Federal Regulations.

In summary the instructions state:

- A sponsor may request orphan drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug.
- A sponsor of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent drug for the same rare disease or condition if a plausible hypothesis can be presented that the subsequent drug may be clinically superior to the first drug.
- More than one sponsor may receive orphan drug designation of the same drug for the same rare disease or

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condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

- A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed, shall be provided.
- A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from non-clinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive, shall be provided. Copies of pertinent unpublished and published papers are also required.
- Where the sponsor of a drug that is otherwise the same drug as an already approved orphan drug seeks orphan drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug shall be provided.
- Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible must be submitted.
- A summary of the regulatory status and marketing history of the drug in the USA and in foreign countries shall be provided, for example Investigational New Drug (IND) and marketing application status and dispositions, what uses are under investigation and in what countries, for what indication is the drug approved in foreign countries, and what adverse regulatory actions have been taken against the drug in any country.

Documentation, with appended authoritative references, to demonstrate that:

1. The disease or condition for which the drug is intended affects fewer than 200 000 people in the USA or, if the drug is a vaccine, diagnostic drug or preventive drug, the persons to whom the drug will be administered in the USA are fewer than 200 000 per year. Or
2. For a drug intended for diseases or conditions affecting 200 000 or more people, or for a vaccine, diagnostic drug or preventive drug to be administered to 200 000 or more persons per year in the USA, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the USA.

   The following Tips for Applying for Orphan Product Designation (Helpful Hints) can also be downloaded from the FDA website (*www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/TipsforApplyingforOrphanProductDesignation/default.htm)*:

   - Format your application so that it is user friendly. Proper formatting of your application is very important. The reviewer of the application needs to be able to 'walk through' your application with ease.
   - Be aware that all nine items in the application will be reviewed, although most critically in two areas: scientific rationale and population prevalence – not to be confused with population incidence!
   - If the product is approved abroad, list the countries where it is approved and for how long. In this case, it is helpful to provide copies of the package insert(s).

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As already mentioned, if a drug has received an orphan drug designation in the USA, the company will be entitled to tax credits on clinical research.

Companies can also receive technical assistance from the Agency pre-authorisation, as well as being eligible for access to a simplification of the administrative procedures (reduction of the waiting period and reduction of the amount of registration fees).

Once approved, a marketing exclusivity of 7 years is granted.

Paediatric drug development and US Orphan Drug Act incentives

The US Office of Orphan Products Development (OOPD) at the FDA has long recognised paediatric patients as 'therapeutic orphans' due to the lack of adequate paediatric dosing information among drugs that are on the market.

In the paediatric population, growth and developmental changes can influence the way drugs are absorbed, distributed, metabolised and excreted, which are vastly different from in adults. Based on these unique pharmacokinetic properties, the OOPD has determined that paediatric patients constitute a unique population that is eligible for orphan designation if the prevalence of the paediatric population with the disease or condition is less than 200 000. With regard to currently marketed drugs with no approved paediatric indication, OOPD will consider a paediatric indication a new 'orphan' indication, for which the sponsor may request orphan drug designation. It should be emphasised that the economic incentives apply only to the clinical paediatric drug development, and the orphan-drug marketing exclusivity applies to the designated paediatric indication of the drug or biological product.

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The OOPD encourages drug sponsors to give attention to the multiple economic incentive provisions of the Orphan Drug Act, including tax credits for clinical research and waiver of the PDUFA application fee, and to obtain orphan drug designation of a drug or biological product intended for paediatric use.

1.6.2 EU application procedures

The EMA website is very useful and provides details of the process and different guidance documents on how to apply for an orphan designation, as well as the incentives available for sponsors developing orphan drugs.

In Europe, there are three distinct regulatory phases that medicines intended for orphan disease must pass through, and these are summarised below:

- Getting the orphan medicinal product designation.
- Obtaining the marketing authorisation through the central procedure. Orphan drugs follow the same procedure as for non-orphan drugs except that the sponsor also needs to show to the Committee for Orphan Medicinal Products (the Committee at the EMA responsible for orphan drugs – further information below) that the product still is within the orphan drug designation. If it is not, the product can still be approved but not as an orphan drug.
- Covering each national health technology assessment (HTA) and pricing reimbursement procedure.

Process to apply for an orphan designation (Europe)

As already mentioned, to qualify for orphan designation in Europe, the following criteria must be met:

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- It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than 5 in 10 000 people in the EU at the time of submission of the designation application.
- It is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition, and without incentives it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development.

In both cases, there must also be either no satisfactory authorised method of diagnosis, prevention or treatment of the condition concerned, or, if such a method does exist, the medicine must be of significant benefit to those affected by the condition (this concept is explored further below).

To apply for an orphan drug designation in Europe, the following steps should be complied with:

1. *Notification of intention to submit*

   More than 2 months in advance of applying for an orphan drug designation, the applicant/sponsor should submit a letter of intent to EMA, who strongly encourages sponsors to also request a pre-submission meeting with the Agency prior to filing an application – preferably 2 months in advance of the filing.

2. *Pre-submission meeting*

   These meetings for orphan designation are free of charge and usually take place via teleconference, unless the sponsor has a strong preference to come to the Agency in person.

   The main sections of the application for an orphan drug designation are:

(a) Description of the condition (orphan designation, medical plausibility, justification of life-threatening or debilitating nature).

(b) Prevalence of the condition.

(c) Potential for return of investment.

(d) Existence of other methods of diagnosis, prevention or treatment (why methods are not satisfactory, or justification of significant benefit).

(e) Description of stage of development.

(f) Bibliography.

The application form does not need to be fully completed before this meeting but the name of the product, the proposed indication, the name and address of the sponsor, and the planned submission date for the designation application should be filled in. It is, however, in the applicant's best interest to have the draft designation application as complete as possible for the meeting.

The application will be discussed with the agency at this meeting, and after the meeting the applicant will have the opportunity to refine the application. This meeting is very useful for the applicant in terms of getting increased insight into and understanding of the requirements as well as identifying areas where the application can be strengthened.

Pre-submission meetings are also useful as the evaluation process has a fixed duration of 90 days without the possibility of a clock stop or the inclusion of additional data. Experience has shown that these meetings have a positive impact on the success rate of the applications.

Applications for orphan designation of orphan medicines are reviewed by the EMA. Once the application is complete, the sponsor should submit the complete

application to the Agency and to the assigned coordinator from COMP. Applications for orphan designation are free of charge.

3. *Submission of application; validation by the Agency (day 1).*
4. *Assessment/COMP meeting/possible hearing/COMP opinion adopted* (by day 60 or day 90). Seventy per cent of requests for orphan designation receive an opinion after 60 days.

   COMP is a committee within EMA that is responsible for evaluating whether a product fulfils the Orphan Drug Criteria and issues an opinion regarding the Orphan Drug Designation. At this stage the drug has not received a designation.

   The composition of COMP

   - a chairman elected by serving COMP members;
   - one member nominated by each of the 27 EU Member States;
   - three members nominated by the European Commission to represent patient organisations;
   - three members nominated by the European Commission on the Agency's recommendation;
   - one member nominated by each of the EEA-EFTA states (Iceland, Liechtenstein, Norway);
   - one European Commission representative;
   - general observers.
5. *Opinion sent to the European Commission.*
6. *Commission decision granted (within 30 days).*
7. *Publication in EU Register on the Commission's website; publication of public summary of opinion on the Agency's website.*

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Parallel application with the USA and Japan

The EMA encourages parallel applications for orphan designation with its international partners, for the benefit of global development of medicines for rare diseases.

If an application has not been submitted in the USA before, the Agency encourages the sponsor to seek orphan designation from both the EMA and the FDA in parallel, using the Common EMA/FDA Application Form for Orphan Medicinal Product Designation, which is available on the EMA website. (This application form is also available on the FDA website and contains detailed notes for completion.)

The EMA provides scientific advice and protocol assistance in parallel with the US FDA. One important topic should be to ensure a correct choice of primary endpoint has been made, to ensure it is in agreement with both the FDA and EMA.

Based on the success of this collaboration between the EU COMP and the FDA, 62% of applications were submitted in parallel in the EU and the FDA in 2012 (*www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/02/news_detail_001718.jsp&mid=WC0b01ac058004d5c1*).

If an application has not been submitted to the Japanese authorities before, the Agency also encourages the sponsor to seek orphan designation from the Ministry for Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). An increase in the number of Japanese orphan drug designations with prior European designations was observed in 2012.

As has already been stated, in order to obtain orphan status in the EU, if a satisfactory method of diagnosis, prevention or treatment of the condition concerned is already authorised in the Community, any subsequent medicine must be of significant benefit to those affected by the condition.

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This begs the question, what is significant benefit?

Significant benefit is defined as a clinically relevant advantage or a major contribution to patient care. Assumptions of potential benefit(s) should be plausible and where possible based on sound pharmacological principles.

In general, a demonstration of potentially greater efficacy, an improved safety profile, and/or more favourable pharmacokinetic properties than existing methods may be considered to support the notion of significant benefit. In addition, a new mechanism of action, an easier route of administration, a reduction in the number of pills or i.v. cycles, etc. may also be accepted, although it is important to note that significant benefit will also need to be confirmed prior to market authorisation to maintain orphan status.

Once a medicine has received a positive opinion on orphan designation from COMP and been granted orphan status by the European Commission, its sponsor is then eligible to benefit from the following incentives:

- Fee reductions: the EMA operates a fee-reduction policy for designated orphan medicinal products.
- Protocol assistance: a form of scientific advice provided by the EMA for sponsors intending to develop an orphan-designated medicinal product for marketing authorisation.
- Access to the centralised authorisation procedure (mandatory) and 10 years of market exclusivity once authorised.
- Community and Member State incentives: an inventory of incentives available for orphan medicines across the EU has been drawn up by the European Commission.

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Requesting protocol assistance

Companies can request protocol assistance either during the initial development of a medicinal product before submission of a marketing authorisation application or later on, during the post-authorisation phase. Protocol assistance is particularly useful to companies developing a medicinal product when:

- there appears to be no or insufficient relevant detail in EU guidelines or guidance documents, or in Pharmacopoeia monographs, including draft documents or monographs released for consultation;
- the company chooses to deviate from the available guidance in its development plan.

Market exclusivity in Europe

- The EMA and Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product.
- This period may be reduced to 6 years if at the end of the fifth year it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity.
- Exceptions:
  - the original Marketing Authorisation (MA) holder gives consent;
  - the original MA cannot supply sufficient product;
  - the second applicant can show that their product is safer, more effective or otherwise clinically superior.

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EU marketing authorisation application for orphan drugs

All human medicinal products, orphan and non-orphan, must be shown to meet defined high standards of quality, safety and efficacy.

For drugs to be approved at the EU Community level (and orphan drugs fall into this category) a dossier must be submitted to the Committee for Medicinal Products for Human Use (CHMP, comprised of scientific staff from the EU member countries) at the EMA. This committee is responsible for evaluating the data presented to determine whether they are sufficient to permit market authorisation. Although a number of guidelines have been developed at the European level, one particular guideline for clinical trials in small populations is of particular relevance to both sponsors and assessors.

An additional step for orphan products is that COMP, as already discussed, will review the significant benefit claimed to ensure that the criteria on which the orphan designation were based remain valid.

The European Commission will grant the final approval of the drug. At this stage the product might not yet be available for patients; for this to happen there need to follow national discussions on price and reimbursement.

The positive outcomes following a request for marketing authorisation are either a full MA valid for 5 years, renewed after re-evaluation of the risk–benefit balance, or alternatively an approval may be granted with conditions. A conditional approval may be granted on the basis of less complete data if it is in the interest of public health and in cases where an unmet medical need of patients exists. However, it is important to be able to show that the medication is associated with a positive benefit–risk ratio for the patient.

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It is not intended for the marketing authorisation to remain conditional indefinitely. A conditional marketing authorisation is valid for one year and can be renewed, although it should be noted that as soon as missing data become available, this should revert to a normal non-conditional MA. A conditional MA is regulated by the EU Guideline EC 726/2004.

There will, however, always be cases when a patient population is so small that comprehensive data may never become available or the present state of scientific knowledge is insufficient, or it would be against generally accepted principles of medical ethics. In these cases it will normally not be possible to assemble a full dossier that fulfils the criteria for a full marketing authorisation. The MA will be reviewed annually to reassess the risk–benefit balance based on follow-up studies including pharmacovigilance studies.

As in the USA, it is also important for prospective sponsors to be aware of the recent paediatric legislation, as although 55% of rare diseases will affect both adults and children, 15–20% affect children only.

The Paediatric Regulation EU REGULATION (EC) No 1901/2006 came into force in the EU in 2007. Its objective is to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years;
- ensuring that medicines for use in children are of high quality, ethically researched and authorised appropriately;
- improving the availability of information on the use of medicines for children.

This legislation applies to all medicinal products and obliges the sponsor to submit a Paediatric Investigation Plan (PIP) to

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the Paediatric Committee (PDCO) at the EMA. This document is legally binding on the sponsor.

If results compliant with the agreed PIP are submitted at the time of marketing authorisation, instead of an extension of the supplementary protection certificate (a way of prolonging the period of market exclusivity created by Council Regulation EEC No 1768/92), the 10-year period of orphan market exclusivity will be extended to 12 years.

Further information can be downloaded from: *http://europa.eu/legislation_summaries/other/l21156_en.htm*

1.7 External links and sources of further information

EMA: guidance and procedural information on applying for orphan designation: *www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp*

EU Rare disease (orphan) designations:

www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp

NIH Office of Rare Diseases Research (ORDR): *http://rarediseases.info.nih.gov/*

US Food and Drug Administration: Developing Products for Rare Diseases & Conditions: *www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm*

US Public Law 107–280—Nov. 6, 2002: Rare Diseases Act of 2002: *http://history.nih.gov/research/downloads/PL107–280.pdf*

Japan Intractable Diseases Information Center: *www.nanbyou.or.jp/english/index.htm*

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2

Characteristics of rare diseases

With additional contributions by Gordana Tankovic

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Abstract: Rare diseases affect only a very small percentage of the population. Most are caused by genetic defects, but environmental exposure during pregnancy or later in life, often in combination with genetic susceptibility, is another cause. Some are rare forms or rare complications of common diseases. Rare diseases are frequently life-threatening or chronically debilitating and are characterised by a broad diversity of disorders and symptoms. The lack of quality information on the disease often results in a delay in diagnosis. Disease management is often complex. Increasing awareness has led to the development of appropriate public health policies.

Key words: rare disease, definition, characteristics, disease management, public awareness.

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2.1 Definition of rare diseases, prevalence, incidence and coverage by the International Classification of Diseases (ICD)

2.1.1 What are rare diseases?

A rare disease is any illness that only affects a limited number of individuals in the population (Schieppati et al. 2008). Definitions vary throughout the regions in the world (see Chapter 1), but all describe primarily proportions of affected patients in a population.[1,2] Other factors, such as the existence of adequate treatments, the severity of the disease or the economic viability of treatments may be additionally included (Wikipedia: rare disease). The expression 'orphan disease' is frequently used synonymously but also applies to the concept that describes diseases that are neglected by the drug industry (Aronson 2006). Some conditions are so uncommon that they have been classified as being ultra-rare, such as Hutchinson-Gilford syndrome (progeria), or Whipple's disease, although this term has no formal legal definition.

Despite this, the UK National Institute for Clinical Excellence (NICE) has stated in their Citizen Council Report on Ultra-Orphan Drugs (2004) that they consider a disease to be classified as ultra-rare if it affects fewer than 20 patients per million of population (i.e. one patient per 50 000). The report is available from *http://tinyurl.com/b3qurp3*.

Alternatively, conditions that initially were classified as rare eventually outgrow that categorisation, for example AIDS, while once common childhood diseases such as mumps became rare due to mass immunisation.

In the USA, a disease is rare if fewer than 200 000 US citizens are affected, as outlined in the ODA of 1983

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(Public Law 97-414). This number corresponds to about 1 in 1500 Americans (7.5/10 000). Additionally, conditions are included that may affect more than 200 000 patients in the USA but for which there is no reasonable expectation that the costs of developing and marketing a treatment drug will be recovered from sales in the USA. With regard to medical devices, any disease is considered rare that occurs so infrequently in the USA that there is no reasonable expectation that a medical device (Humanitarian Use Device, HUD) for treating such disease will be developed without applying provisions of the ODA that help to make development easier (Humanitarian Device Exemption) and less costly.

In the EU, rare diseases were defined by the European Commission on Public Health as life-threatening or chronically debilitating diseases that are of such low prevalence that special combined efforts are needed to address them. According to regulation EC 141/2000 (European Parliament and the Council 2000), presence of the condition in fewer than 5 people per 10 000 is regarded as the threshold of a low prevalence. Medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition may be eligible even when the prevalence is higher if the return on investment is so low that development is not feasible.

The World Health Organization (WHO) defines a rare disorder as all pathological conditions affecting 6.5–10 out of every 10 000 inhabitants. The Japanese law considers a rare disease as one that affects fewer than 50 000 patients or about 1 in 2500 people (4/10 000) (Hayashi and Umeda 2008), while Australia sets limits at 2000 Australian patients or about 1 in 10 000 people (in addition to products that are otherwise not commercially viable) (Lavandeira 2002). Though absolute numbers are related to the population sizes

of the respective countries, there is a considerable variation in the ratio. In Asian countries, legal definitions were implemented, for example, in Taiwan (2000) and Korea (2005). Mexico just recently in 2012 defined a rare disease as one affecting no more than 5 in 10 000 individuals.

Additionally, lists of diseases of different extent are provided, mostly including genetic disorders, which are regarded as being rare by the US National Organization for Rare Disorders with about 1200 items, or by the US Office of Rare Diseases with over 6000 entries.

Further information can be found in the Orphanet Report on Prevalence of rare diseases: bibliographic data:

www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf

2.1.2 Prevalence and incidence

Despite being individually infrequent conditions, rare diseases affect a significant portion of the general population when considered as a class. There are between 5000 to 8000 distinct rare diseases, and there are estimates that about 25 million patients in the USA and approximately 6–8% of the total EU population, that is, between 27 and 36 million people are affected. This is equivalent to around 250 000 people or fewer for each disease throughout the 27 EU Member States (EMA – Press Office 2007: EMEA/290072/2007). This overall prevalence is similar to that of type 2 diabetes mellitus and Knight and Senior (2006) point out that they were unable to find original data on which these estimates were based.

According to estimates published by the Raising Rare disease Awareness, Research and Education (R.A.R.E.) Project (*http://rareproject.org*), over 350 million people have rare diseases worldwide. The majority of rare diseases have

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only a few sufferers and 80% of all rare disease patients are affected by just 350 rare diseases.

However, it is challenging to get agreement on these figures, and according to the NIH there are nearly 7000 rare diseases, while the EMA estimates that rare disease affects nearly 250 million people worldwide – a significant portion of which are genetic in origin and afflict children.

Very little documented information on the epidemiology of rare diseases is available, and the exact prevalence of individual rare diseases is unknown or difficult in most instances to assess from public data sources. Moreover, on average, 250 new diseases are described each year in the medical literature (EMA – Press Office 2007: EMEA/290072/2007).

Incidence[3] data (the number of new cases in a population) may be derived from birth registries or calculated[4] from prevalence and vice versa, although it should be noted that even this is difficult, given the inadequacy and heterogeneity of disease coding from country to country.

Finding prevalence[5] data can be similarly challenging, although the publication on the EMA website of a document entitled 'Relevant sources for orphan disease prevalence data' should now facilitate this process:

www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500130297.pdf

The prevalence of rare diseases or the reported number of published cases from bibliographic data has been summarised recently and estimated to be in the range of 0.005 (e.g. Refsum disease) to 50 (e.g. Noonan syndrome) per 100 000 (Aymé 2011). Some diseases are reported only as case studies or only affect a few families.

The prevalence of rare diseases can also vary between populations. A disease that is rare in some populations may be common in others. In inherited disorders, founder effects

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(as observed with Finnish disease heritage or inherited disorders of Ashkenazi Jews) can result in a disease that is very rare worldwide being prevalent within the smaller community, while frequently occurring infectious diseases in a given geographic area may be rare everywhere else. Leprosy is a rare disease in France but common in central Africa. Thalassemia, which is a form of anaemia of genetic origin, is rare in Northern Europe, whereas it is frequent in the Mediterranean region. Most rare forms of cancer have no apparent pattern of geographic distribution. Cancer in children is generally considered a rare condition, though the same cancer may be common in adults (Wikipedia: rare disease).

Rare cancer diseases (see section 2.5.3) represent approximately 20% of all cases of malignant neoplasms (ESMO 2008). Though genetic aetiologies of rare diseases are the largest group, currently most orphan drug applications concern rare forms of cancer.

2.1.3 Classification and disease coding of rare diseases

The International Classification of Diseases (ICD) is a standard diagnostic classification for all general epidemiological studies, many health management purposes and clinical use developed by the WHO. The current version is the ICD-10, which was endorsed by the Forty-third World Health Assembly in May 1990 and came into use in WHO Member States from 1994.

Most rare diseases are absent in ICD-10. Those which have a specific code assigned are disseminated across ICD chapters and may even be misclassified (Aymé et al. 2010). The introduction of the coding category 'other secondary pulmonary hypertension' (416.8) in ICD-10 appeared to

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lead to a sudden decline in the reported mortality from Idiopathic Pulmonary Arterial Hypertension in the category 'primary or idiopathic, pulmonary hypertension' (416.0), which was used as a default for both conditions in ICD-9 (Gomberg-Maitland 2011; Link et al. 2011). Lack of specific categories impedes the registration of patients in national or international databases and leads to under-reporting of rare diseases in morbidity and mortality data in public health statistics.

A WHO Topic Advisory Group (TAG) on rare diseases was established to contribute to the revision process of ICD-10. A new dedicated chapter in ICD-11 for multisystem diseases will be proposed. Specific default codes will be created for rare diseases, to allow them to be identified as such in order to improve statistics about rare diseases. Revised chapters will follow a primarily clinical approach, only secondarily an aetiological one, up to the gene level. When several names are possible for a disease, descriptive names formed in accordance with a clinical approach are preferred. Rare diseases affecting several body systems will be included in every relevant chapter as ICD-11 will be poly-axial, but a main code is proposed to allow for alignment according to the most severe involvement and/or the most likely involved clinical specialty taking care of the management of the disease. In some cases, the choice is open to debate. The rare disease community is taking an active role in the revision process. All the revised chapters that are open for comment are available on the website of the European Union Committee of Experts on Rare Diseases (EUCERD; see Chapter 5) (*www.eucerd.eu*).

To overcome current difficulties with medical coding of rare diseases, Orphanet (an EU web portal for rare diseases and orphan drugs; see Chapter 4) has established a partnership with the WHO to ensure a fair representation of

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rare diseases in general. In order to prepare the proposal, Orphanet has collected all published expert classifications and established a database of phenotypes indexed with ICD-10 codes, MIM codes (Mendelian phenotypes), genes, mode of inheritance, age of onset and class of prevalence. Phenotypes are assigned to as many classification systems as necessary to represent them. The visualisation of the classification systems and of the place of each disease within the classification is available on the Orphanet website. The Orphanet nomenclature of rare diseases is commonly accepted, directly exploitable by information systems and available on request. It will soon be released as an open-source service.

In addition to this effort to update ICD, the Orphanet inventory of diseases is cross-referenced with other nomenclatures, namely SnoMed-CT and MeSH, through collaboration with the . The alignment of the Orphanet nomenclature with the Online Mendelian Inheritance in Man (OMIM) codes of the US National Center for Biotechnology Information (NCBI) poses the question of the fair representation of genetic diseases and of the genetic contribution of genomics to disease definition, in relation to the needs of the end users.

2.2 Characteristics of rare diseases, genetics and underlying causes

Rare diseases are serious, mainly chronically and/or progressively disabling, and can be life limiting and life threatening (Melnikova 2012). Rare diseases lead to a marked reduction in the patients' quality of life and impose a considerable socio-economic burden. Symptoms of some rare diseases may appear at birth or in childhood, including

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spinal muscular atrophy, lysosomal storage disorders, patent ductus arteriosus (PDA), familial adenomatous polyposis (FAP) and cystic fibrosis. More than half of rare diseases appear during adulthood, such as renal cell carcinoma, glioma and acute myeloid leukaemia.

According to estimates published by the R.A.R.E. Project (*http://rareproject.org*), 75% of rare diseases affect children. Most rare diseases have no existing effective cure. Rare diseases are responsible for 35% of deaths in the first year of life, and approximately 30% of children with a rare disease have a life expectancy of less than 5 years.

Approximately 80% of rare diseases have identified genetic origins, and affect between 3% and 4% of births (EMA – Press Office 2007: EMEA/290072/2007). Other rare diseases are due to degenerative and proliferative causes or they may be the result of infections, rare cancers, autoimmune diseases or congenital malformations. Genetic alterations ranging from point mutations (e.g. cystic fibrosis) to deletion of whole chromosomes may be involved (e.g. Ullrich-Turner syndrome).

A detailed text discussing, in detail, various causes of rare diseases was published by the US Institute of Medicine in 2010 (Field and Boat 2010).

Diversity and heterogeneity of rare disease vary not only from disease to disease but also within the same disease. Despite belonging to the same disease, on the genetic level every family may display a unique genetic alteration. Reduced penetrance and variable expressivity are factors that influence the effects of the particular genetic changes and therefore the same alteration can lead to different clinical manifestations from one affected patient to another.

Detailed medical and scientific knowledge about rare diseases is frequently lacking. The number of scientific publications about rare diseases continues to increase,

particularly those identifying new syndromes. However, fewer than 1000 diseases benefit from even minimal amounts of scientific knowledge (EMA – Press Office 2007: EMEA/290072/2007). These tend to be the rare diseases that occur most frequently.

2.3 Common problems encountered with rare diseases

Rare diseases exhibit quite diverse pathologies, but they share some common features in addition to their rareness that are particularly striking from the patients' perspective.

EURORDIS has listed common problems faced by patients with rare diseases and their families, as summarised below:

> *Beyond the diversity of the diseases, rare disease patients and their families are confronted with the same wide range of difficulties arising directly from the rarity of these pathologies:*
>
> - *Lack of access to correct diagnosis: the period between the emergence of the first symptoms and the appropriate diagnosis involves unacceptable and highly risky delays, as well as wrong diagnosis leading to inaccurate treatments: the pre-diagnosis maze;*
> - *Lack of information: about both the disease itself and about where to obtain help, including lack of referral to qualified professionals;*
> - *Lack of scientific knowledge: this results in difficulties in developing therapeutic tools, in defining the therapeutic strategy and in shortage of*

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therapeutic products, both medicinal products and appropriate medical devices;

- *Social consequences: living with a rare disease has implications in all areas of life, whether school, choice of future work, leisure time with friends, or affective life. It may lead to stigmatisation, isolation, exclusion from social community, discrimination for insurance subscription (health insurance, travel insurance, mortgage), and often reduced professional opportunities (when at all relevant);*
- *Lack of appropriate quality healthcare: combining the different spheres of expertise needed for rare disease patients, such as physiotherapist, nutritionist, psychologist, etc . . . Patients can live for several years in precarious situations without competent medical attention, including rehabilitation interventions; they remain excluded from the health care system, even after the diagnosis is made;*
- *High cost of the few existing drugs and care: the additional expense of coping with the disease, in terms of both human and technical aids, combined with the lack of social benefits and reimbursement, cause an overall pauperisation of the family, and dramatically increases the inequity of access to care for rare disease patients.*
- *Inequities in availability of treatment and care: innovative treatments are often unevenly available in the EU because of delays in price determination and/or reimbursement decision, lack of experience of the treating physicians (not enough physicians involved in rare diseases clinical trials), and the absence of treatment consensus recommendations.*

(EURORDIS 2005 p. 7)

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Getting a correct diagnosis is often a major challenge for someone who has a rare disease. Lack of awareness among health professionals, unspecific disease symptoms, and unavailability of technologies for diagnosis may contribute to this situation. Common clinical conditions are more frequently expected by diagnosticians and patients with rare diseases are perceived as surprising when they are encountered by the physician.[6]

Rare diseases are frequently complex and involve multiple body systems, and patients may be seen by several medical specialists who do not have the 'full picture'. In a survey published by EURORDIS in 2004, of 5980 patients suffering from one of eight rare diseases, delayed diagnosis was a major issue: in total, 25% of respondents reported waiting between 5 and 30 years from onset of symptoms to a confirmed diagnosis. An initial wrong diagnosis was reported by 40% of respondents, which led to inappropriate surgery (16%), medication (33%) or psychological care (10%). Approximately 25% of patients had to travel to a different region to obtain the confirmatory diagnosis, and 2% had to travel to a different country. Nearly half of the respondents reported a poor communication about the diagnosis. The genetic nature of the disease was not communicated to the patient or family in 25% of cases. On the other hand, 80% of patients or their parents spontaneously engaged in a debate with the family to help diagnose or prevent other cases (EURORDIS 2004).

Trying to obtain medicines can be distressing for some patients or there may be no treatment at all. Primary healthcare providers frequently provide insufficient information to patients with rare diseases and sometimes lack knowledge on the specific condition.

These problems are likely to have a negative impact on the patients' quality of life and potentially their life expectancy.

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They can also often result in a huge waste of public health resources due to inefficient usage (Gatta et al. 2010).

2.4 Patient care, management and counselling

The goal in the management of rare disease patients is to obtain the highest attainable standard of health and to provide necessary resources to overcome common obstacles in their lives. However, the medical services that patients with rare diseases receive are often poorly coordinated, inequitable and unsatisfactory. The many families affected by these conditions frequently struggle to access the support, care and help they need (Gatta et al. 2010).

As inherited disorders may affect whole families, genetic counselling is paramount when communicating the diagnosis. Early diagnosis before onset of irreversible organ damage is crucial for early treatment (if available). Patients frequently report not being offered psychological support in relation to their condition or assistance with their non-medical needs. In many instances, patients are not provided with enough information on research and on clinical trials into their condition. Communication between members of the multidisciplinary team involved in care of the patient is frequently missing.

Centres of Expertise and European Reference Networks (ERNs) (see Chapter 5: European Project for Rare Diseases National Plans Development, EUROPLAN) are considered key elements in the EU for providing high-quality care and multidisciplinary management of patients with rare diseases. The Directive of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (2011/24/EU) provides for the

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development of ERNs. The European Commission proposes Member States establish Centres of Expertise. The first set of EUCERD Recommendations on Quality Criteria for Centres of Expertise for rare diseases in EU Member States were adopted unanimously in 2011. The recommendations cover the mission and scope of the Centres of Expertise, the criteria for designating Centres of Expertise, the process of designating and evaluating national Centres of Expertise, and the European dimension of Centres of Expertise. Centres should provide multidisciplinary treatment capacities including qualified laboratories, ensure integrated medical care, combine research, training and clinical care, and collaborate with national and international patient organisations.

Similarly, patient advocacy groups such as NORD in the USA as well as EURORDIS in the EU make information on centres of excellence generally available to individual patients. Additionally, NORD maintains a database of clinical experts that can be suggested to newly diagnosed patients. Without these valuable resources, newly diagnosed rare disease patients often visit general practitioners who are greatly lacking published information about the primary care role in rare diseases (Knight and Senior 2006). NORD also regularly publishes Physician Guides that centralise care and treatment information for a specific rare disease. These have just recently been updated to an electronic format, and can be downloaded from:

http://nordphysicianguides.org/nordphysicianguides.org

The perceived risks of establishing Centres of Expertise (or in the USA, Centers of Excellence) are lack of local medical expertise and most importantly the incapacity to provide patient-centred, holistic care, which is important in the medical care of patients with chronic debilitating or potentially fatal conditions.

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2.5 Examples of rare diseases

In the following section, some examples of rare diseases are given. The selection is somewhat arbitrary, but includes rare diseases that are typical for their general features, have importance in that larger groups of patients are affected, are illustrative examples for the aetiology or may exemplify a treatment modality. As the goal is not a comprehensive description of the individual disease, the reader should refer to relevant textbooks and journals for further details.

2.5.1 Genetic and inherited diseases

Genetic and inherited disorders are the biggest group of rare disease. Various genetic alterations such as point mutations, trinucleotide repeats, microdeletion syndromes or missing or additional chromosomes may be involved.

Rett syndrome

Rett syndrome (Matijevic et al. 2009) was first described in 1966 by the Austrian paediatrician Andreas Rett. It is a progressive brain disease nearly always exclusively seen in females, which leads to mental impairment, autism, gait disturbance and loss of control of the hands.

After apparent normal development of variable duration during the first year of life, development seems to stop and thereafter acquired walking and speech may be lost, sometimes with a sudden onset and stereotypic hand movements (wringing, putting hands into the mouth) may appear. This phase may stabilise over years or spasticity with secondary spinal scoliosis and breathing problems as well as epileptic seizure may develop. Affected individuals can frequently not communicate by speech with their family and

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caregiver. Stereotypical hand movements can make eating a very difficult task.

The estimated prevalence ranges from 1 in 10 000 in Scotland to 1 in 23 000 in the USA. It is a genetic disease related to the X chromosome (methyl CpG-binding protein 2 gene) but is almost exclusively a new mutation, probably from paternal male germ cells. As the father would pass on only the Y chromosomes to male progeny, they will not be affected, (but daughters receiving the X chromosome will, and both the paternal and maternal X chromosome may be silenced in a variable percentage).

In animal models, neurological deficits could be reversed upon restoration of gene function. There is currently no cure in humans. The only available treatments are supportive and include occupational therapy, speech and physical therapy. The life expectancy may be up to 50 years or more.

Further information is available from the International Rett Syndrome Foundation (*www.rettsyndrome.org*), the NIH (*www.ninds.nih.gov/disorders/rett/detail_rett.htm*), Rett UK (*www.rettuk.org*) and others.

Cystic fibrosis

Cystic fibrosis (mucoviscidosis) (Culling and Ogle 2010; Garattini et al. 2011) is one of the most common inherited disorders in Caucasians. The estimated prevalence in Europe is about 1/10 000 individuals. The cystic fibrosis gene is located at 7q31-32 on chromosome number seven and spans about 280 kilo base pairs of genomic DNA. In most Caucasians (70%), three base pairs (nucleotides) in exon 10 of this chromosome are deleted (F508del; stop codon).

Five additional mutations cover the majority of cases (85%). Up to 27 exons must be sequenced to find uncommon mutations. The disease has an autosomal recessive genetic

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trait, that is, symptoms will occur if both the maternal and paternal gene copy are defective, and there is a 25% risk of siblings being affected as well.

Caused by a faulty gene (Cystic Fibrosis Transmembrane Conductance Regulator; CFTR), the chloride ion channel of the exocrine glands is dysfunctional. As a consequence, mucus becomes thick and sticky, which blocks airways and provides a substrate for bacterial growth in the lungs, thus leading to recurrent infections. Progressive breathing difficulty is typical. Sweat will become very salty (defective reabsorption) and electrolyte imbalances may result (hyponatraemia). In the pancreas, scarring and cyst formation occurs, which finally may lead to diabetes. Liver cirrhosis with bile duct obstruction may occur and fatty stools (steatorrhoea), malnutrition and poor growth may result. Male patients are normally infertile and the disease can make it harder for women to get pregnant. Infrequently (15%), disease onset is very early in life, which then is characterised by constipation in newborns (meconium ileus).

The life expectancy depends on disease severity but is generally reduced. Even in the more severe cases it has increased continuously from death in late childhood to currently 30 years or much more. Though the disease affects multiple organs, the limiting factor is frequently deteriorating lung function.

Lifelong prophylactic use of one (tobramycin) or more antibiotics is necessary. Orphan medications like aerosolized dornase (recombinant human deoxyribonuclease, Pulmozyme®) help to break down DNA in mucus, thus decreasing its viscosity. Sometimes, lung transplantation may become the last resort. Gene therapy for the pulmonary aspects of cystic fibrosis in humans is feasible. Ivacaftor is a recently approved (2012) drug that repairs chloride channel transport and may help in some cases (5%) of cystic fibrosis.

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Other drugs for more frequent mutations are under development (e.g. Ataluren, VX-809).

Further information is available from the NIH (*www.nhlbi.nih.gov/health/health-topics/topics/cf/*), the Cystic Fibrosis Foundation (*www.cff.org/*), the European Cystic Fibrosis Society (*www.ecfs.eu/*) and others.

Friedreich's ataxia

Friedreich's ataxia (Koeppen 2011; Marmolino 2011) is an inherited (autosomal recessive) progressive spinocerebellar ataxia. The disease onset is typically before the age of 20 years with uncoordinated movements, gait disorder, slurred speech, muscle weakness or paresis mainly of legs. Visual impairment (50% of patients with optic nerve atrophy), diabetes mellitus (30%), hearing impairment, and frequently fatal hypokinetic cardiomyopathy may occur. Curvature of the spine is frequent and may need surgical stabilisation with metal rods. Decreased vibratory sense, lost proprioception, and absent deep tendon reflexes are found as the myelin sheath of particularly sensory neurons gets progressively lost during the course of the disease. Inability to walk alone is common 10 to 20 years after disease onset.

The disease occurs in about 1 in 100 000 newborns. The underlying gene defect was mapped to chromosome 9, and in 1996 several mutations in the X25 (FXN) gene were described. While in healthy adults only 7–20 copies of the intronic GAA triplet are found, a repeat expansion of 200–900 copies is seen in patients, which blocks the synthesis of the protein frataxin by interfering with transcription (gene silencing). Frataxin is found in mitochondria. Disease models of frataxin deficiency (in mice, drosophila and yeast) have provided inconclusive results.

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Some researchers found diminished activity of malate dehydrogenase, overload with mitochondrial iron, and accumulation of reactive oxygen species, while others did not. Treatments targeting reactive oxidative species (e.g. idebenone) were not clinically effective.

There is currently no cure or effective treatment for Friedreich's ataxia, although some symptoms can be treated with physical therapy to prolong the use of the arms and legs, orthopaedic surgery for scoliosis, and diabetes or heart medication for these co-existing problems.

Further information is available from the NIH (*www.ninds.nih.gov/disorders/friedreichs_ataxia/detail_friedreichs_ataxia.htm*), the Friedreich's Ataxia Research Alliance (*www.curefa.org/*), Ataxia UK (*www.ataxia.org.uk/pages/friedreichs-ataxia.html*) and others.

Huntington's disease

Huntington's disease (Novak and Tabrizi 2011; Reiner et al. 2011) is an autosomal dominant progressive neurodegenerative disorder characterised by unwanted choreatic (involuntary jerky) movements, muscle rigidity, and cognitive decline (dementia). The patient may find increasing difficulties in feeding, and problems with chewing and swallowing may lead to choking or weight loss. Difficulty speaking, sleep disturbances, psychiatric abnormalities, and memory deficits are all associated symptoms. The onset of the disease is usually between 35 and 44 years of age. Disease complications such as aspiration pneumonia, heart disease, injury from falls, and suicide reduce life expectancy to approximately 20 years after manifestation of the first symptoms.

The prevalence in the Caucasian population is estimated at 5–10 cases per 100 000 persons. It is much more common in

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people of Western European descent than in those of Asian or African ancestry, and local clusters have been described (Venezuela, Tasmania, Wales and Sweden).

The disease is caused by expansion of nucleotide triplet repeats (CAG coding for glutamine) in the Huntington gene on the short arm of chromosome 4 (4p16.3) with 40–100 copies found in patients, fewer than 30 copies in healthy adults, and both sick and healthy individuals found in the intermediate range. Disease onset is earlier with a higher number of trinucleotide repeats. With successive generations, the number of repeat copies increases (genetic anticipation). New mutations occur infrequently. In patients, an altered Huntingtin protein is formed (expanded polyglutamine strand with a putative toxic gain of function), which gradually leads to selective neural cell loss (apoptosis) in the brain (caudate nucleus and putamen).

There is no cure for Huntington's disease. Choreatic symptoms can be treated with dopamine receptor blockers (tetrabenazine), rigidity with antiparkinsonian drugs (amantadine), and myoclonic hyperkinesia with valproic acid. Feeding tubes (PEG) may be necessary to manage malnutrition. Disease progression leads to complete dependency in daily life and full-time care of bedridden patients is finally required. In a transgenic mouse model, caspase inhibitors (e.g. minocycline) showed promise to reduce cell death in Huntington's disease. Stem cell therapy for replacement of damaged neurons is another investigational treatment.

Further information is available from the NIH (*www.ninds.nih.gov/disorders/huntington/huntington.htm*), the Huntington's Disease Society of America (*www.hdsa.org/*), Huntington's Disease Association UK (*http://hda.org.uk/*) and others.

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Fragile X syndrome (Martin-Bell-syndrome)

Fragile X syndrome (D'Hulst and Kooy 2009; Heulens and Kooy 2011) is the most common inherited intellectual disability. It affects 1 in 4000 boys and 1 in 6000 girls of all races. The disease is characterised by mild to moderate mental retardation, sometimes hyperactivity, social anxiety or autism, distinct facial features (including elongated face, protruding ears, and prominent jaw), hyperextensible finger joints, flat feet, and low muscle tone. Cluttered speech and self-talk are commonly seen. Recurrent otitis and sinusitis are common during early childhood. Mitral valve prolapse and strabismus may occur. The risk of seizures is increased. Affected individuals have a normal life expectancy.

The disease has an X-linked dominant trait with reduced penetrance in females, that is, females having a second, normal X chromosome are normally less affected. Males may additionally display prematurely large testicles (macrogenitosomia praecox, macroorchidism). Analysis of family histories shows the presence of asymptomatic male carriers with their grandchildren affected by the condition thus suggesting genetic anticipation. In most cases, the disorder is caused by the unstable expansion of CGG repeats (>200) and abnormal methylation in the *5′* untranslated promoter region of the FMR1 gene in the X chromosome, which results in decreased gene transcription and protein expression. The FMRP protein is found throughout the body but in highest concentrations within the brain and testes where it is required for normal development and regulation of the metabotropic glutamate receptor pathway.

Cytogenetic diagnosis by culturing cells in a folate-deficient medium for chromosomal analysis reveals a thin

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(apparently fragile) satellite-like structure in chromosome band Xq27.3 as a consequence of the abnormal methylation pattern in 10–40% of cells. This method is outdated and replaced today by molecular genetic diagnosis (sequencing).

Treatment with drugs, such as stimulants and selective serotonin re-uptake inhibitors (SSRIs) (for anxiety, obsessive-compulsive behaviours), and atypical antipsychotic agents (for self-injury, aggressive behaviours, and autism) is being combined with speech therapy, sensory integration occupational therapy, individualised educational plans, and behavioural interventions. Targeted investigational treatments (mavoglurant, dipraglurant, fenobam, arbaclofen, minocycline) are also currently being studied.

Further information is available from the NIH (*http://rarediseases.info.nih.gov/gard/6464/fragile-x-syndrome/resources/1*), National Fragile X Foundation (*www.fragilex.org/*), Fragile X Research Foundation of Canada (*www.fragilexcanada.ca*), the Fragile X Society (*www.fragilex.org.uk/*) and others.

Phenylketonuria (Følling's disease)

Phenylketonuria (Blau et al. 2010; van Spronsen 2010; van Spronsen and Enns 2010) is an autosomal recessive metabolic genetic disorder characterised typically by a point mutation in the phenylalanine hydroxylase gene (chromosome 12q22-q24.1) rendering the enzyme non-functional (missense and nonsense mutations).

This means that the amino acid phenylalanine is not metabolised to tyrosine and accumulates to reach potentially toxic concentrations that may impair postnatal cognitive development. Otherwise, because of a lack of precursors, melanine synthesis is affected and children with the condition

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are blond, fair skinned, have blue eyes and are sensitive to light (phototoxicity, eczema). Phenylalanine is partially converted via a salvage pathway to phenylpyruvate, which is excreted in the urine.

Children appear normal at birth because they are protected by the maternal metabolic capacity. However, if left untreated, phenylalanine builds up when proteins are consumed and children lose interest in their surroundings, exhibit irritability, peculiarities of gait, stance and sitting posture, increased deep tendon reflexes, a peculiar 'mousy' odour, and vomiting over the following months, and by one year of age, they become progressively mentally delayed. Epilepsy and seizures are sometimes present.

The estimated prevalence is about 1/15 000 births. The disease is more frequent in Caucasians (of Celtic descent) and Native Americans than in other racial groups. Neonatal screening (bacterial bioassay, tandem mass spectrometry) is conducted to identify hyperphenylalaninaemia as onset of mental retardation is preventable in this disease.

Current treatment is a lifelong special diet of foods with a markedly reduced amount of phenylalanine (casein hydrolysate) immediately after birth, though a small amount is essentially needed for normal development. Affected patients may not eat high-protein foods, such as meat, milk, eggs, and nuts, but fruits and vegetables. The artificial sweetener aspartame is metabolised to phenylalanine, while cyclamate may be consumed safely. Maintaining compliance with permanent dietary restrictions may be challenging in the management of this disease.

Further information is available from the NIH (*http://rarediseases.info.nih.gov/gard/7383/phenylketonuria/resources/1*), The National Society for Phenylketonuria (*www.nspku.org/*), the European Society for Phenylketonuria and Allied Disorders (*www.espku.org/*) and others.

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Pompe's disease

Pompe's disease (glycogen storage disease type II) (Jamil et al. 2011; Tager et al. 1987; van der Ploeg and Reuser 2008) is an autosomal recessive metabolic disorder caused by accumulation of glycogen in the lysosomes throughout the body (skeletal muscle, heart, liver, brain). It is caused by various mutations (chromosome 17q23; most frequently a point mutation in a splice site); the acid maltase, which converts glycogen into glucose, is deficient.

The infantile-onset form is usually diagnosed at 4–8 months and is characterised by hypotonia, swallowing difficulties, hypertrophic cardiomyopathy and hepatomegaly. If left untreated, death occurs within 2 years. The adult form presents as progressive limb-girdle myopathy beginning with both legs and finally affecting the respiratory muscles. Wheelchair and respiratory assistance are needed in end-stage disease.

The estimated disease incidence is about 1/57 000 for the adult form and 1/138 000 for the infantile form.

Cardiac and respiratory complications are treated symptomatically. Physical and occupational therapy may be given. Since 2006, recombinant human alglucosidase alfa (Myozyme®, Genzyme) has been available as an intravenous infusion for the early onset disease. Enzyme replacement therapy (ERT) prolongs ventilator-free survival and overall survival in patients with infantile-onset. Commonly observed adverse reactions to treatment are pneumonia, respiratory complications, infections and fever. Serious reactions include heart and lung failure and life-threatening allergic responses. Myozyme® therapy costs approximately $300 000 a year and lifelong substitution therapy is needed. Additional therapy is needed to decrease antibody formation against the enzyme.

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More recently, alglucosidase alfa for the treatment of late-onset disease was approved by the FDA (in 2010) after a successful scale-up of the manufacturing process (in Chinese hamster ovary cells) and is now marketed as Lumizyme® (Genzyme).

Further information is available from the Muscular Dystrophy Association (*www.mdausa.org*), the Acid Maltase Deficiency Association (*www.amda-pompe.org*), The Association for Glycogen Storage Disorders (*www.agsdus.org/*), the International Pompe Association (*www.worldpompe.org*) and others.

Gaucher disease

The disease was first described by Philippe Gaucher in 1882. Gaucher disease (Chen and Wang 2008; Martins et al. 2009; Messner and Cabot 2010) is the most frequent lysosomal storage disease and has an autosomal recessive trait (1q21). As glucosylceramidase is deficient, glucocerebroside which results as residue from turnover of cell membranes accumulates in macrophages and organs (liver, spleen and bone marrow). Clinical symptoms of bone marrow depression occur include bruising, fatigue, anaemia as well as bone pain, osteoporosis, yellowish skin and scleral deposits, as well as enlargement of the liver and spleen.

Three clinical forms can be distinguished:

- *Type I* (or non-neuropathic type), which presents in 95% of all cases with patients living well into adulthood.
- *Type II* (or acute infantile neuropathic disease), in which patients present with progressive brain damage (epilepsy, dementia, ataxia, myoclonus, hypertonia, ocular muscle apraxia) and for which typically a fatal outcome by 2 years of age is observed.

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- *Type III* (chronic neuropathic form), which is slowly progressive and in which patients present with mild neurological symptoms and with patients dying as teens.

The prevalence of Gaucher disease in the general population is around 1 in 60 000–100 000, but type I is considerably more frequent among Ashkenazi Jews. Heterozygote carriers have an increased risk of developing Parkinson's disease.

Biochemical abnormalities such as high levels of alkaline phosphatase, angiotensin-converting enzyme, and immunoglobulin may assist in the diagnosis. Lysosomal enzymes (tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase) may be elevated. Sequencing of the beta-glucosidase gene or measurements of glucocerebrosidase activity in circulating leukocytes are confirmatory tests.

Specific treatments for Gaucher disease have been developed. In 1991, placenta-derived Ceredase® was approved as the first specific treatment for the disease. An improved ERT of Chinese hamster ovary cells with intravenous recombinant glucocerebrosidase (imiglucerase) (Cerezyme®) was approved in 1994 for type I and type III disease. Treatment must be given as an intravenous infusion every other week. During the first year of therapy, antibodies to imiglucerase are formed in approximately 15% of the treated patients. These patients have a higher risk of hypersensitivity reactions including anaphylactoid reactions. Velaglucerase alfa (VPRIV®) is another human glucocerebrosidase enzyme for ERT which was approved in 2010, and in 2012 a further alternative became available with the approval of taliglucerase alfa (Elelyso®) in the USA.

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Imiglucerase is efficient in reducing visceral and haematological consequences of the disease, but response to skeletal disease manifestations is slow. In patients with established brain damage further deterioration of cerebral function is not effectively reduced as the protein does not cross the blood–brain barrier. With enzyme replacement, annual treatment costs of approximately US$200 000 per patient occur. Therefore it is proposed to apply the minimal-effective dose rather than the maximally tolerated dose in order to minimise the economic burden on society, if the difference between high-dose and lower-dose regimens is clinically meaningless (Zimran 2011).

An alternative treatment strategy is substrate reduction therapy (SRT) by inhibition of the glucosylceramide synthase as with the orally administered miglustat (Zavesca®), which is used for treatment of mild-to-moderate type I disease for which ERT is not an option (Cox et al. 2003; Ficicioglu 2008; Weinreb et al. 2005). Though oral drug administration may be more convenient to patients requiring lifelong therapy, diarrhoea occurs in 80% of patients as an undesirable drug effect.

Bone marrow transplantation is risky in Gaucher patients and hence rarely performed, but it introduces beta-glucosidase expressing monocytes which is therefore a curative treatment.

2.5.2 Environmentally caused rare diseases

New and emerging viral diseases are the most important environmental causes of rare diseases. As regional differences exist, frequent conditions in one region may be quite uncommon in another one, which may lead to misdiagnosis, sometimes with fatal outcome. RNA viruses play a prominent

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role in emerging diseases as the high error rates of the polymerases that replicate their genomes make it easier for them to adapt to varying conditions. Environmental and social changes, for example as a result of human activities (deforestation, irrigation, mass tourism, import of foreign crop material, war) can disturb the host–viral equilibrium and accelerate viral traffic (Geisbert and Jahrling 2004; Morse 1997).

Babesiosis

Babesiosis (Boustani and Gelfand 1996; Homer et al. 2000) is a worldwide occurring tick-borne protozoal disease of wild and domestic animals (dogs (*Babesia canis*), cattle (*Babesia divergens*), and rodents (*Babesia microti*)). Vectors differ between geographic areas and host species (*Dermacentor reticulates, Ixodes scapularis, Boophilus microplus*).

In 1888, Babes described some intraerythrocytic 'bacteria' as having caused the deaths of 30 000–50 000 head of Romanian cattle due to febrile haemoglobinuria. More than 100 *Babesia* species infect animals, but as most species are host specific (e.g. *B. canis*), human infection has been associated with only a few species. Infection via contaminated blood infusion (humans) or via transplacentary infection (livestock) is possible. Human infection is generally rare and mainly restricted to some endemic areas in Europe, North-eastern America, Korea, Japan and Australia. As the clinical course (fever, shaking chills, haemolysis, haemoglobinuria) and the diagnostic blood smear resemble malaria, misdiagnosis is frequent, and a high degree of medical suspicion is needed to consider this possibility and finally to avoid a fatal outcome.

Most patients are asymptomatic and may need only supportive care; some patients develop high-spiking fever,

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headaches and arthromyalgia. Splenic infarction or rupture may occur as complications. Asplenic, elderly and other immunocompromised patients are at greatest risk for severe disease. Infections with *B. divergens* tend to be more severe than those with *B. microti*, and secondary renal impairment may occur. The overall mortality rates for symptomatic cases are less than 10%. Though generally not well tolerated, the first line treatment is a combination of clindamycin and quinine. An alternative treatment regimen is atovaquone plus azithromycin. Exchange transfusion may be performed in more severe cases.

Further information is available from the US Centre for Disease Control (*www.cdc.gov/parasites/babesiosis*) and others.

Marburg haemorrhagic fever

Marburg virus disease is haemorrhagic fever caused by a filovirus, which normally affects non-human primates. The disease first appeared in Europe in 1967 after importing green monkeys (grivet; *Chlorocebus aethiops* (which today is a species protected by the International Union for Conservation of Nature (IUCN) Red List of Threatened Species) from Uganda to Marburg) (Slenczka and Klenk 2007). Small outbreaks occurred first in Marburg and Frankfurt and, about 4 weeks later, in Belgrade after laboratory workers at the former vaccine manufacturer Behringwerke became accidentally exposed to infected tissues. Monkey kidney cell cultures were used for the production of poliomyelitis vaccine at that time.

As the clinical symptoms of patients were not very alarming during the first 3–4 days, the first patients were treated in their homes for up to 10 days in spite of symptoms that included sudden onset of malaise, myalgia, headache and

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high fever. Gastrointestinal symptoms (nausea, vomiting and diarrhoea) made healthcare professionals think of dysentery or typhoid fever, and patients were admitted to hospital. Most patients had developed conjunctivitis, exanthema and increased transaminases. During the second week after onset of disease, white blood cells and platelets decreased, petechiae occurred and finally patients were bleeding from all body orifices and puncture sites. In some cases, patients died from severe haemorrhagic shock on the day after hospital admission. Mental confusion and paraesthesias eventually occurred. Relapses with hepatitis, uveitis, orchitis with virus persisting in semen were seen in the convalescent phase. As for numerous other haemorrhagic fevers (Lassa fever, Junin fever, Machupo virus, Kyasanur forest disease, Sabiá virus, Omsk Haemorrhagic Fever, Crimean-Congo haemorrhagic fever, Hantavirus, Rift Valley fever, Ebola, dengue, yellow fever, to name a few), only supportive care is possible. Secondary infections were rare (needle-stick injuries) and tertiary infections did not occur.

In total, 31 people became infected and seven of them died during that outbreak. The hitherto unknown virus was isolated within 3 months. The natural reservoir of the virus is believed to be the fruit bat.

More recent outbreaks were reported from African countries (South Africa, Kenya, Congo, Uganda and Angola) and from former Soviet Union laboratories (who tried using the virus for weaponisation). Nowadays, heightened awareness of bioterrorism has changed the perspective towards the need to search for vaccines against haemorrhagic fevers, which earlier have been considered as infrequent local outbreaks in remote areas.

Further information is available from the US Centre for Disease Control (*www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/marburg.htm*) and others.

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2.5.3 Rare cancer disease

Cancer is a leading source of morbidity and mortality, with breast, lung, bowel and prostate cancer the most frequently found in Western societies. Regarding the burden of rare tumours, there is still no generally accepted definition to measure it. A consensus proposal was to set the threshold incidence at 6/100 000/year (Gatta et al. 2010).

Hairy cell leukaemia (HCL)

Hairy cell leukaemia (HCL) (Forconi 2011; Galani et al. 2012; Golomb 2011) is a rare chronic lymphocytic leukaemia (CLL) with accumulation of abnormal B-lymphocytes in bone marrow, spleen and peripheral blood. The estimated incidence is 1 in 500 000 per year and the disease is more frequent in males and patients with advanced age.

Normal blood cell production is affected, which leads to anaemia (causing symptoms like fatigue), leukopenia (causing e.g. recurrent infections), thrombocytopenia (which may lead to mild bruising) and finally bone marrow failure. Hairy cells produce tumour necrosis factor-alpha, which further suppresses normal blood cell production. Massive hepatosplenomegaly frequently results in abdominal discomfort and sometimes splenic rupture. The cause of the disease is unknown, but recently recurrent somatic mutations have been detected (BRAF V600E) (Tiacci et al. 2011).

The diagnosis is made from bone marrow aspiration or blood with tartrate resistant acid phosphatase staining or flow cytometry. Treatment is generally delayed until symptomatic disease occurs and then typically it is initiated as monotherapy. First-line therapy is chemotherapy with purine analogues (cladribine, pentostatin). Immunotherapy with B cell monoclonal antibodies (rituximab, alemtuzumab, ibritumomab) or interferon alpha is a second-line option.

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Red blood cell transfusions are sometimes necessary as supportive treatment. Splenectomy may produce long-term remission in some cases. Bone marrow transplants may also be considered in younger patients. Disease-free remission may last 10 years or longer, although the risk of developing other cancers or autoimmune disease is increased. Lifelong monitoring is necessary.

Further information is available from the US National Cancer Institute (*www.cancer.gov/cancertopics/pdq/treatment/hairy-cell-leukemia/Patient/page1*), Hairy Cell Leukemia Consortium (*www.hairycell.org*) and others.

ALK-positive non-small cell lung cancer

Non-small cell lung carcinoma (NSCLC) (Kwak et al. 2010; Morris et al. 1994; Shaw et al. 2009; Soda et al. 2007) accounts for approximately 80% of all lung cancers. The incidence of NSCLC is higher in Caucasians compared with Asians or South Asians (57.7, 29.8 and 12.0 per 100 000, respectively). NSCLCs are relatively insensitive to chemotherapy and radiation therapy, and lung surgery is the treatment of choice if diagnosed in early stage. However, approximately 75% of newly diagnosed NSCLC patients already have advanced (stage III or IV) disease. Hence, the overall 5-year survival with lung cancer is low (about 15% in US patients), and this further decreases with advanced stage. In a small subgroup (1% to 4.9% in unselected NSCLC populations, 3% to 13% with enrichment strategies) of patients with NSCLC, the EML4-ALK fusion oncogene is found.

This fusion results from inversion within a chromosome (2p23), which leads to expression of a chimeric tyrosine kinase of echinoderm microtubule-associated protein-like 4 (EML4) fused to the kinase domain of the anaplastic lymphoma kinase (ALK). Since the mid-1990s it has been

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known that ALK is a tyrosine kinase receptor (2p23) that is thought to be normally dormant but is aberrantly activated in a variety of malignancies. As a molecular target in lung cancer it was recognised much later when Mano (2008) reported that 6.7% of Japanese patients with NSCLC carry the EML4 fusion oncogene. The EML4-ALK gene fusions occur almost exclusively in carcinomas arising in non-smokers or light smokers and are more frequent in adenocarcinoma and younger patients. The presence of an ALK rearrangement is diagnostically detected with a molecular probe (by fluorescence in situ hybridisation; FISH). This diagnostic test helps to identify the rare genetic subgroup of putative treatment responders.

Crizotinib (Xalkori®) is a recently approved novel small molecule ALK inhibitor, which showed response rates of 54–61% of ALK-positive NSCLC patients and a progression-free survival approaching 10 months. Other available treatments include erlotinib (Tarceva®) and pemetrexed.

Further information is available from the US National Cancer Institute (*www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/Patient*), My Cancer Genome (*www.mycancergenome.org*), the National Lung Cancer Partnership (*www.nationallungcancerpartnership.org/*), the Bonnie J. Addario Lung Cancer Foundation (*www.lungcancerfoundation.org/*) and others.

Pseudomyxoma peritonei

Pseudomyxoma peritonei (Baratti et al. 2009; Deraco et al. 2004; O'Connell et al. 2002; Witkamp et al. 2001) is caused by scattered tumour cells producing abundant mucin, which builds up in the intraperitoneal cavity and progressively compresses abdominal and pelvic organs. The disease typically originates from a perforated appendiceal epithelial tumour

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(MUC2 expressing goblet cells). The K-Ras (p53) gene is probably involved in the oncogenesis. The estimated incidence is approximately 1/1 000 000/year. The disease onset is usually after the age of 40 years and more frequently affects females.

Symptoms include abdominal distension, weight changes, constipation, vomiting and dyspnoea. As symptoms are unspecific or initially missing and as the condition is rare, initial misdiagnosis or incidental diagnosis during surgery for other conditions is frequent. The diagnosis may also be made by computerised tomography and confirmed through pathology. As the tumour is slow growing, 'watchful waiting' is frequent, and treatment strategies include cytoreductive surgery (visceral resections and peritonectomy, i.e. removal of ovaries, tubes, uterus, intestine and other affected organs such as gallbladder, spleen, small intestine, stomach) with intraperitoneal hyperthermic chemotherapy (IPHC) or early post-operative intraperitoneal chemotherapy (EPIC), typically with mitomycin C. Recurrence after complete tumour removal may occur. The 20-year survival rate for non-aggressive peritoneal pseudomyxoma may reach 70% with optimal treatment, but it is still a fatal disease.

Further information is available from the PMP Awareness Organization (*www.pmpawareness.org*), PMP PALS' Network (*www.pmppals.org/pseudomyxoma-peritonei.html*), Pseudomyxoma Survivor UK (*www.pseudomyxomasurvivor.co.uk*) and others.

2.6 Public awareness and disease support groups

Public awareness of rare diseases is slowly increasing since the introduction of orphan drug legislation in the USA, the EU and other regions.

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In the USA, the ORDR at the NIH was established in 1993 in order to coordinate public research and information on rare diseases. In 2002, the US Congress passed the Rare Diseases Act, 19 years after the 1983 Orphan Drug Act. More recently (2012), the FDASIA gives the FDA the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biologics, while PDUFA V authorises the FDA to collect fees from companies that produce certain human drug and biological products. These additional funds play an important role in expediting the drug approval process.

European regulations and new policies in place aim to facilitate the development of treatments for rare diseases, including the EU Regulation on Orphan Medicinal Products (1999), the EU Regulation on Paediatric Drugs (2006), the Programme of Community Action in the Field of Public Health (2007–2013) and the EU Seventh Framework Programme (FP) for Research (2007–2013).

In 2007, the European Commission's Directorate General for Health and Consumers (DG SANCO) launched public consultation regarding European action in the field of rare diseases at the 4th European Conference on Rare Diseases (ECRD) 2007, held in Lisbon, Portugal. Hundreds of stakeholders participated in the consecutive public consultation process. The Council Recommendation on Rare Diseases was finally adopted by the European Council on 8 June 2009; it recognises rare diseases as a public health priority (European Council 2009: Council Recommendation 2009/C 151/02). The EU funded the Orphanet database of rare diseases, centres of excellence, and patient-support groups.

Numerous national and international non-governmental organisations are operating worldwide to provide support to

patients and to encourage research in the field of orphan diseases.

EURORDIS (see Chapter 3) is a non-governmental patient-driven alliance of patient organisations. EURORDIS aims to improve the quality of life of people living with rare diseases in Europe through advocacy at the European level, support for research and drug development, networking patient groups, raising awareness and other actions designed to fight against the impact of rare diseases on the lives of patients and family.

Rare Disease Day is one public initiative with annual events since 2008 coordinated by EURORDIS at the international level and the National Alliances of Patient Organisations at the national level. The sixth international Rare Disease Day was held on 28 February 2013 and was organised with rare disease national alliances in 24 European countries. Hundreds of patient organisations from more than 60 countries contributed with awareness-raising activities.

NORD (see Chapter 3) was established in 1983 by individuals and families with rare diseases in the USA and is dedicated to helping patients and assisting the organisations that serve them. **Genetic Alliance**, established in 1986, is a health advocacy organisation in the USA and provides information on approximately 1200 rare diseases and support groups. The **R.A.R.E. Project** is a US fundraising charity founded in 2011, which tries to build a strong international community and worldwide network between patients scattered by the rarity of their conditions irrespective of their geographic location. The **Global Genes Project** in the USA is an initiative of the **R.A.R.E. Project** and intends to raise public awareness of the millions of families affected by rare disease around the world.

The Canadian Organization for Rare Disorders (**CORD**) (see Chapter 3) is the national network that represents people affected by rare disorders within Canada.

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It is frequently reported that patients and families affected by rare diseases suffer from a great deal of isolation and the opportunity to meet with or talk to other affected families is hugely appreciated and beneficial. Disease support groups may help to establish contacts with other affected patients and their families. Patient support organisations are often a major source of information for patients about their rare disease.

Comprehensive information on patient organisations is provided in Chapter 3.

2.7 Resources and external links

Patients with common diseases may have various treatment options, while patients with rare diseases must educate themselves about the availability of therapies and sometimes even educate their primary care physician. Patients with rare diseases and families generally show an appreciation of the importance of clinical research and have a high motivation to participate in clinical trials related to their condition. Therefore, a collection of resources and external links is provided.

Database of rare diseases at Orphanet: *www.orpha.net/consor/cgi-bin/Disease.php*

EURORDIS: *www.eurordis.org*

Genetic and Rare Diseases Information Center (GARD) of the US NIH: *www.rarediseases.info.nih.gov/GARD/Default.aspx*

The Global Genes Project Global Genes Project for Rare Disease: *www.globalgenesproject.org*

Health On the Net Foundation (available in several languages, for patients and medical professionals): *www.hon.ch*

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Health-EU Portal: Rare Diseases in the EU: *http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm*

NIH Rare Diseases Clinical Research Network (RDCRN): *http://rarediseasesnetwork.epi.usf.edu*

Orphan Diseasome (Orphan Disease Network (ODN); Orphan Disease Gene Network (ODGN); Orphan Disease Gene Interactome (ODGI)): *http://research.cchmc.org/od/*

Project OrphanAnesthesia – Anaesthesia recommendations for patients suffering from rare diseases: *www.orphananesthesia.eu*

2.8 Notes

1. The prevalence of a disease in a statistical population (e.g. 100 000 adults) is the ratio of the total number of affected patients (irrespective of disease state) in the population at a given time to the total number of individuals in the respective population.
2. The incidence is the proportion of new cases of a disease within a specified time period (e.g. one year) in a statistical population (e.g. 100 000 adults) at risk (of acquiring the disease).
3. For congenital diseases with birth-onset, prevalence = incidence at birth × (patient life expectancy/general population life expectancy); for the other rare diseases, prevalence = incidence × rare disease mean duration.
4. A frequently cited bon mot by Dr Theodore Woodward at the University of Maryland School of Medicine in Baltimore coined in the 1940s says 'when you hear hoof beats behind you, don't expect to see a zebra'. However, that caution against making surprising diagnoses may not be valid in the individual case as the odds of being present or not do not change in a single patient (Harvey et al. 1979).

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3

Patient network and advocacy groups

With additional contributions by Chris Wilson

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Abstract: Though not unique to the field of rare diseases, patient engagement and empowerment through the establishment of patient networks and advocacy groups is of special importance in this field. Patient organisations are currently active in many ways: they increase public awareness, collect information about rare diseases, provide support and information to affected families, encourage basic research and grant funds, maintain patient registries and collections of specimens in biobanks, and network with universities, industry, and health authorities. Numerous organisations are working nationally, internationally, worldwide or virtually. The two biggest umbrella patient organisations are EURORDIS in Europe and NORD in the USA. Most recently, these two groups have signed a strategic partnership agreement to align their activities even more effectively.

Key words: patient networks, organisations, advocacy groups, empowerment, EURORDIS, NORD.

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3.1 Patient empowerment through international institutions: WHO and EU

Patient empowerment has for a long time been of particular relevance within the field of rare diseases. This is mainly due to the specifics of rare diseases, that is, they are chronic and difficult to manage. Thus, coordinated efforts are needed both in relation to research, as well as policy issues, in order to drive progress (Aymé et al. 2008). For example, the WHO sees the empowerment of patients as a prerequisite for efficient and effective healthcare management (WHO 1988; WHO Regional Office for Europe 2012). Thus, it encourages a proactive approach towards partnership among the various stakeholders and promotes patient self-care strategies that eventually lead to better health outcomes and improved quality of life among the chronically ill. The role of independent patient groups is crucial both in terms of their direct support to patients living with the disease and their relatives as well as their substantial contributions to improving care and treatment for other rare disease patients.

At the European level, the EU Council recommends that Member States shall 'consult patients and patients' representatives on the policies in the field of rare diseases and facilitate patient access to updated information on rare diseases' as well as 'promote the activities performed by patient organizations, such as awareness raising, capacity building and training, exchange of information and best practices, networking and outreach to very isolated patients' (European Council 2009: Council Recommendation 2009/C 151/02, Article VI (18) and (19)).

The European communication thus pointed out the changed role of patients, which led to patient representatives on COMP and opened the door to patient involvement in

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EMA interactions with patient organisations in other areas such as pharmacovigilance.

3.2 The role of patient organisations and advocacy groups: the needs, strategies, objectives and achievements

The objective of patient organisations or support groups is to improve quality of life for patients and their families who are affected by a certain disease. Their objectives include raising public awareness of a disorder, dissemination of information about the disease and its treatment, and promotion of scientific research. Organisations may also serve as a facilitator between the patient and the professionals.

Patient organisations not only bring together patients and families of patients suffering with a certain disease, they can also often lead initiatives towards a better recognition and understanding of the condition. By working closely with regulatory authorities, industry representatives and healthcare experts, they are often instrumental in driving development and access to appropriate treatments. As many rare diseases go undiagnosed or misdiagnosed for years, and since even with the proper diagnosis, in most cases not all physicians have enough knowledge and understanding of each rare disease, patients with rare diseases as well as their families and caregivers are often able to supplement a detailed understanding of the symptomatic complexities associated with their diseases.

Patient organisations and advocacy groups support patients with rare diseases in various activities:

- to enable interpatient exchange of personal experiences with the disease;

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- to facilitate access to disease-related information and, if available, to treatment;
- to drive research towards better care and treatment of the disease; and
- to represent the interests of patients in the political decision-making process.

Disease-specific patient organisations are, by nature, representative of a small number of patients affected by the condition. However, there are many shared challenges and experiences among the various rare diseases patient advocacy and support groups. When the more than 5000 to 8000 rare disorders are combined, rare disease support groups represent the needs of approximately at least 5% of the world population. Umbrella organisations of the various patient advocacy groups such as NORD in the USA, EURORDIS in Europe, and others around the world play an essential role in promoting public awareness, patient empowerment, access to affordable treatment on behalf of the entire rare disease community and the different disease-specific patient organisations. Patient organisations also often defend and demand the right of patients to make health policy decisions that have an impact on their own disease.

Patient organisations and patient advocacy groups can make a real difference when it comes to realising access to orphan drugs. NORD and EURORDIS have been very much involved in developing the Orphan Drug Legislation/Act in the USA and the EU, respectively. COMP was the first committee at EMA to have patient representatives as full committee members (see Chapter 1).

Patient organisations and advocacy groups often take an active and influential role in raising awareness of their disease and of opportunities to participate in clinical trials. Advocacy groups have a critical function in educating the reimbursement community. Early engagement with patient groups also helps

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pharmaceutical companies to better understand patients' needs and to tailor programmes to address them.

There are national alliances of rare disease patient organisations in many countries throughout the world. In its 2012 report, EUCERD mentions that there are 2376 disease-specific patient organisations registered in Orphanet, the portal for rare diseases and orphan drugs.

Overarching umbrella organisations consolidate the numerous alliances (see section 3.4). EURORDIS runs the Council of National Alliances of rare disease patient organisations in Europe. NORD allies numerous national organisations with each other in the USA. These groups collaborate and work closely on common global issues, policies and awareness-related initiatives such as the Rare Disease Day (see Chapter 2).

3.3 Patients and research: patients' engagement and empowerment within rare diseases

Out of necessity and a lack of adequate support for rare diseases as a public priority, patient groups often provide and indeed need access to research and development resources. As awareness about rare disease is still limited and knowledge about the natural history of these conditions is frequently incomplete, engaged patients and patient organisations are a major catalyst in promoting academic research and industrial development regarding a specific rare disease. This is accomplished by raising awareness though industry collaborations, conferences and social media, but most importantly through involvement in the drug development process (e.g. specimens for biomarker development, study participants, historical control groups and sources of

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funding). An example of the active role of patient support groups is the spectrum of participants during the EURORDIS 10-year anniversary workshop 'Gaining access to rare disease research resources', which consisted of 75% rare disease patient representatives compared with 25% researchers, healthcare professionals, industry representatives, and public policymakers. The main outcome of the meeting was the formulation of basic requirements for collaborations between patients and EU decision-makers and the need to intensify the study of the natural history of rare diseases and disease impact on the patients' quality of life.

Additionally, EURORDIS facilitates the preparation of European Public Assessment Reports (EPARs) in the review process of marketing authorisation applications of new medicines for rare diseases.

Similarly, NORD provides support to industry for basic research and development of orphan drug products. NORD works closely with both the NIH and FDA to establish policies that facilitate sound rare disease research and efficient, safe and effective orphan drug development. Most recently, NORD was profoundly involved in policy efforts to pass the Affordable Care Act, the PDUFA and the FDASIA (for further detail, please see Chapter 5).

3.4 Umbrella organisations: EURORDIS and NORD

3.4.1 European Rare Diseases Organisation (EURORDIS)

EURORDIS (*www.eurordis.org/*) is a patient-driven alliance of patient organisations representing more than 510 rare diseases patient organisations in over 48 countries, 2012 EUCERD Report.

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The mission of EURORDIS is to build a strong pan-European community of patient organisations and of the people living with rare diseases, to be their voice at the European level, and to fight against the impact of rare diseases on affected patients' lives.

Activities run by EURORDIS include, but are not limited to, raising public awareness of rare disease and promoting scientific and clinical research in the field of rare diseases. EURORDIS is also active in several policymaking initiatives and has representatives in agencies such as the European COMP and the PDCO, as well as the European network for Health Technology Assessment (EUnetHTA).

By way of example, as early as December 2000 EURORDIS was amongst the first of the stakeholder groups (including academia, industry and other patient groups) to carry out advocacy work to support and help drive the adoption of the EU Regulation on Paediatric Drugs in 2006 and the adoption of the EU Regulation on Advanced Therapy Medicinal Products (e.g. gene therapy, stem cell therapy, cancer vaccines) in 2007. Since that time EURORDIS has contributed to many additional legal frameworks, including, for example, the Cross Border Health Care Directive.

EURORDIS is also a partner in several other large-scale projects that will affect research, drug development and the lives of rare disease patients, for example the European Patients' Academy on Therapeutic Innovation (EUPATI), the European Platform for Rare Disease Registries (Epirare) (see section 6.4), RD-Connect (an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research) and RareConnect, an online environment created by EURORDIS and NORD, where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources (for more information, please refer to the next section).

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EURORDIS reviews all public summaries of COMP opinion documents on applications for orphan drugs designation as well as the EPARs and liaises with the patient groups concerned (see Chapter 4).

Through the different national advocacy groups, EURORDIS is also active at national levels and encourages the implementation of national plans or strategies for rare diseases in European countries (EUROPLAN; see Chapter 5).

EURORDIS issues position papers on key issues for the European rare disease community and distributes them to the EU regulatory authorities and decision-makers (e.g. Clinical Added Value of Orphan Medicinal Products (CAVOMP) and Patients' Rights in Cross-Border Health Care; see Chapter 7). EURORDIS also provides various support services to individual patients, for example helplines and summer schools. EURORDIS collaborates with NORD and other patient organisations such as CORD, at the international level.

3.4.2 National Organization for Rare Disorders (NORD)

NORD (*www.rarediseases.org/*) is the US federation of voluntary health organisations helping people with rare diseases. NORD was established in 1983 by patients and families who worked together to get the Orphan Drug Act passed (see Chapter 1).

The mission of NORD is to help people with rare orphan diseases and assist the organisations that serve them. 'NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.' (*www.rarediseases.org/about/vision-mission*)

NORD is dedicated to helping the nearly 30 million Americans with rare diseases, and the organisations that serve

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them, through programmes of education, advocacy, research and patient services. NORD works closely with many other organisations in the rare disease community, for example EURORDIS and government agencies such as the NIH and the FDA. Like EURORDIS, NORD provides information for patients and families. NORD mentors patient organisations, advocates for sound policies on behalf of the entire rare disease community, sponsors research grants, and runs patient assistance programmes. NORD is also initiating a patient registries programme in response to a great need expressed by rare disease patients for guidance and common tools to collect patient-reported information. The registries programme will represent an integral element of the organisation's larger strategy to increase research and knowledge in the field of rare diseases through the establishment of a Center for Rare Disease Research and Development (CRDR).

NORD's information service includes referral to disease-specific information, assistance in finding high quality information on the Internet, and facilitating the exchange of experiences and best practices of existing and newly formed patient organisations through regional meetings. Please refer to the NORD website for more information.

NORD provides information about opportunities to participate in clinical trials, although NORD does not endorse or recommend any specific clinical trials. NORD also provides information about rare diseases, through publications, its website and other educational offerings. A compendium of over 1200 patient friendly, rare disease reports has been developed for patients and their families, which includes information on symptoms, causes, treatments, clinical trials, and links to other sources of help. NORD publishes a growing collection of expert booklets for physicians on selected rare diseases, which can be downloaded from *http://nordphysicianguides.org/*

NORD entered a strategic partnership with EURORDIS in 2009, aligning the organisations in their advocacy efforts, partnering on the RareConnect project and Rare Disease Day, and coming together to represent the 60 million rare disease patients on both continents.

RareConnect (*www.rareconnect.org/en*), the Rare Disease Communities project, is a patient-led social network. The project results from a partnership between EURORDIS and NORD. RareConnect is patient-driven and communities are created by dedicated patient organisations. Moderators represent people with real experience with their disease. The online community cannot be deleted at the whim of a creator. Sensitive patient data are owned and secured by EURORDIS and NORD. More than 100 patient organisations from over 20 countries have joined.

3.5 National European organisations

Austria

Pro Rare Austria: *www.prorare-austria.org/*

Belgium

Rare Diseases Organisation Belgium: *www.radiorg.be/*; information in Dutch and French

Bulgaria

National Alliance of People with Rare Diseases (NAPRD): *www.rare-bg.com/*

Croatia

The Croatian Society of Patients with Rare Diseases: *www.rijetke-bolesti.hr/*

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Denmark

Rare Disorders Denmark: *www.sjaeldnediagnoser.dk*; information in Danish and English

France

French Rare Diseases Alliance: *www.alliance-maladies-rares.org/*

Germany

German National Alliance for Chronic Rare Diseases (ACHSE): *www.achse-online.de/*

Greece

Greek Alliance of Rare Diseases (PESPA): *www.pespa.gr/*; information in Greek and English

Hungary

Hungarian Federation of People with Rare and Congenital Diseases – Rare Diseases Hungary (HUFERDIS): *www.rirosz.hu/*

Ireland

Genetic and Rare Disorders Organisation (GRDO): *www.grdo.ie/*

Italy

Italian Federation for Rare Diseases (UNIAMO): *www.uniamo.org/*; information in Italian and English

Italian National Centre for Rare Diseases: *www.iss.it/cnmr/*; information in Italian and English

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Luxembourg

Luxembourg Association for Neuromuscular and Rare Diseases (ALAN): *www.alan.lu/alan/*

The Netherlands

Dutch Genetic Alliance (VSOP): *www.vsop.nl/*

Portugal

Portuguese Alliance of Rare Disease Associations: *http://aliancadoencasraras.org/*

Portuguese Federation of Rare Diseases (FEDRA): *www.fedra.pt/*

Romania

Romanian National Alliance for Rare Diseases (RONARD): *www.apwromania.ro/*

Russian Federation

National Association of Rare Diseases Patients: *www.rarediseases.ru/*

Russian Patients Union – Rare Diseases and Orphan Drugs: *http://rare-diseases.ru/*

Spain

Spanish Rare Disease Federation (FEDER): *www.enfermedades-raras.org/*

Sweden

Rare Diseases Sweden (Sällsynta diagnoser): *www.sallsyntadiagnoser.se/*

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Switzerland

Proraris: *www.proraris.ch/*; information in German, French, and Italian

United Kingdom

Genetic Alliance UK is the national charity of over 150 patient organisations: *www.geneticalliance.org.uk/*

Rare Diseases UK (RDUK) is the national alliance for people with rare diseases: *www.raredisease.org.uk/*

Contact a Family for families with disabled children – Rare disorders: *www.cafamily.org.uk/*

The rare disorder team brings together groups, families and individuals of all ages who are affected by rare disorders, including those with late-onset conditions. The Directory of Specific Conditions and Rare Disorders provides descriptions of hundreds of diseases and information on inheritance patterns, prenatal diagnosis, and related organisations. Support is provided through an international web-based confidential linking service for individuals and families with rare disorders.

3.6 Other organisations working in the Americas

3.6.1 Canadian Organization for Rare Disorders (CORD)

CORD (*www.raredisorders.ca/*) is Canada's national network for organisations representing patients with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research,

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diagnosis, treatment and services for all rare disorders in Canada.

3.6.2 Mexican Federation for Rare Disorders (FEMEXER)

Federación Mexicana de Enfermedades Raras (FEMEXER; *www.femexer.org*) provides information on rare diseases to patients, helps with making the diagnosis, provides some financial support to obtain medical care for those in need, and assists in the location of specialist medical treatment.

3.6.3 Geiser Foundation (Argentina)

Fundación GEISER (*www.fundaciongeiser.org/*) is a non-governmental organisation working since 2002 to support Argentinian patients with rare diseases. The website of the foundation provides general information on rare diseases and orphan drugs and publishes online news on these topics in Spanish.

3.6.4 Brazilian organisations

In Brazil, general support for patients with rare diseases is given by the Instituto Baresi (*http://institutobaresi.com/*) and the Rare Disease Study Group (Grupo de Estudo de Doenças Raras, GEDR; *http://estudandoraras.blogspot.com/*) as well as by the Instituto Canguru (*www.institutocanguru.org.br/*) for patients with inborn errors of metabolism.

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3.7 Organisations working in Africa, Asia and Australasia

3.7.1 South African Foundation for Rare Disorders (SAFRD)

The South African Foundation for Rare Disorders (SAFRD; *www.safrd.co.za/*) was established to help support those affected by rare disorders. The Foundation is creating a network to provide assistance to patients and their families and friends. Patients diagnosed with a rare disorder can have access to the emotional support of fellow patients, share their experiences of living with their disorder, and may help to expand knowledge about their disease. The Foundation aims to support patients in living with their disease in the most positive way.

3.7.2 SORD (Japan)

The Supporting Organization for Patients of Rare Disorders in Japan (SORD; *https://www.sord.jp/*) is a non-profit organisation working in Japan to support patients with rare diseases.

Rare diseases in Japan are referred to as 'intractable diseases'. This is not a specifically or clearly defined medical term, but it is used in this context to indicate a 'challenging' or 'incurable' disease defined as:

- diseases that have resulted from an unidentifiable cause and, without a clearly established treatment, have a considerably high risk of disability; and
- diseases that chronically develop and require a significant amount of labour for the patient's care, causing a heavy burden on other family members of the patient, both financially and mentally.

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When a disease fits both definitions of 'intractable' and 'rare', it is called a 'rare disease'. A shortcoming of this definition is its dependence on the current medical standard of therapy and social context. For example, tuberculosis used to be 'intractable' as it was fatal for infected persons before antituberculotic drugs became available.

The mission of SORD is:

- to make all the underlying rare disease patients in Japan visible and connect them with patients of the same disease to bridge the information gap;
- to develop an environment where patients can build reciprocal relationships with clinicians/researchers.

Like other national patient organisations, SORD supports the empowerment of patients to make their own informed decisions. SORD assists patients in finding other patients affected with the same disease through 'Re:me', a social networking service dedicated to rare disease patients. SORD has also initiated some basic research activity: the Patient-driven Rare Diseases iPS Genome Information Bank Project (PRiG Project).

After creation of a patient organisation dedicated to a specific disease, SORD offers help to collaborate on the international level. In the case where no information on a disease is available in Japan, SORD will retrieve international information on the disease, patient organisations, and research institutes.

3.7.3 Australasian Genetic Alliance (AGA)

The Australasian Genetic Alliance (AGA; *www.australasiangeneticalliance.org.au/*) is a network of patient organisations that represent genetic support groups,

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individuals and families in the Australasian region who are living with a genetic condition or a genetic predisposition. With regard to genetic support groups and services operating in an Australian state, the respective alliance members hold further information.

3.7.4 Association of Genetic Support of Australasia (AGSA)

The Association of Genetic Support of Australasia Inc. (AGSA; *www.agsa-geneticsupport.org.au/*) has been active since 1988 and offers support, including seminars, sibling workshops, telegroup counselling, regular newsletters and a family day for patients with inherited diseases. The rare disease register of AGSA represents over 1200 rare conditions.

3.7.5 New Zealand Organization for Rare Disorders (NZORD)

New Zealand Organization for Rare Disorders (NZORD; *www.nzord.org.nz/*) has a network of 147 support groups and helps people affected by rare disorders and their families to find essential information. Like other organisations, NZORD provides resources and information for rare disease patients and support groups, monitors rare disease issues and policy matters, and builds partnerships between patients/families, support groups, clinicians, researchers, policymakers and industry. NZORD was established in 2000, as the result of a conference of over 30 rare disease support groups.

The NZORD mission is:

- to support and improve the level of organisation and information among patients and families affected by rare disorders;

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- to promote research and education that will identify rare disorders early and ensure the best clinical care for the patient and best social support for the family;
- to build partnerships of patients/families, clinicians, researchers, government and industry, that accelerate the research effort towards control and cure of rare disorders.

NZORD supports the formation of patient groups by informing patients of the benefits of advocacy groups and by assisting them in developing their networks. NZORD helps patient groups to establish international collaborations with international patient groups in order to improve access to information and research opportunities.

NZORD also focuses on the improvement of clinical care of patients with rare diseases, promotes newborn screening programmes for early diagnosis of rare disorders, encourages measures to maintain continuity of care in the transition from paediatrics to adult healthcare services for those with complex and chronic disorders, and supports initiatives for improved training of medical practitioners in genetics and genetic counselling.

Since its foundation, NZORD has lobbied for a specialist metabolic service for New Zealand to provide expert advice and specialist medical care for those affected by rare and complex metabolic conditions. Their activities are very similar to the European National Plans. NZORD is a key player in the New Zealand Carers Alliance and supports Government plans to develop a Carers' Strategy for New Zealand.

3.7.6 Taiwan Foundation for Rare Disorders (TFRD)

The mission of the Taiwan Foundation for Rare Disorders (TFRD; *www.tfrd.org.tw/english/*) is to improve the life of

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rare disease patients. TFRD assists rare disease patients in receiving proper medical treatment or rehabilitation, makes orphan drugs and special nutrients available, and helps rare disease patients to get access to education, employment and long-term care.

As a representative for rare disease patients in Taiwan, TFRD advocates the adoption of relevant legislation to ensure rare disease patients' rights, to encourage research on rare diseases, and to increase public awareness of rare diseases.

3.7.7 Malaysian Rare Disorders Society (MRDS)

The Malaysian Rare Disorders Society (MRDS; *www.mrds.org.my/*) was formed in 2004 with the help of the Genetic Unit, Department of Paediatrics, University of Malaya Medical Centre. MRDS supports patients and families that are affected by a rare disorder. The society works to increase awareness of rare disorders through providing information to educate individuals, families, medical professionals, schools, organisations and the general public. The society produces factsheets and newsletters on rare disease topics.

MRDS helps to establish networks between individuals and families with rare disorders, the relevant organisations, professionals, education and intervention centres.

3.7.8 Rare Disease Foundation of Iran (RADOIR)

Established in 2010, the Rare Disease Foundation of Iran (RADOIR) is a private institution that provides services for

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rare disease patients in Iran. Its aim is to improve the quality of life of rare disease patients and to increase public awareness about the burden of rare diseases on patients, their families and the community.

Because of uncertainty about the number of rare diseases and patients in Iran, RADOIR collaborates with the medical system and research centres to provide an information bank of rare disease patients and to disseminate information about rare diseases to health professionals and patients, their families and the general public.

Further information can be found at:
www.radoir.com

3.8 Other patient alliances

3.8.1 European Genetic Alliances' Network (EGAN)

See Chapter 4.

3.8.2 Genetic Alliance (USA)

See Chapter 4.

3.9 Organisations dedicated to a specific disease

The number of disease-specific patient organisations that exist is substantial. NORD lists 1200 patient organisations in its database and Orphanet over 1600 in Europe.

Rather than try to provide a comprehensive list, the reader is directed to the following websites:

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EURORDIS: *www.eurordis.org/*

NORD: *http://rarediseases.org/*

Orphanet: *www.orpha.net/consor/cgi-bin/index.php*

ORDR: *http://rarediseases.info.nih.gov/*

3.10 Virtual health communities

In the early days of the Internet, patient organisations used this medium to inform affected patients and families about their disease, to spread news about novel treatment options or ongoing patient trials, and to help affected families find and contact specialist health professionals.

Today, the evolution of the web and its interactive capabilities has resulted in the emergence of virtual health communities. In these virtual discussion platforms, users can share personal experiences, exchange opinions, and receive social support by the patient community. The virtual communities are becoming an important source of information for patients in making informed and responsible decisions about their health management. Affected users who share the same condition or health problem can often inform each other how they have dealt with certain aspects of their illness or disease in daily life. Virtual communities can share knowledge, resources, and news from different organisations, healthcare professionals, caregivers and patients. Each user can share his or her area of expertise concerning a particular issue with the rest of the network.

Information is power. Patients with chronic and disabling diseases are frequently the most active, engaged and well-informed patients as knowledge of alternative experimental treatments or compassionate use programmes may dramatically improve their quality of life or time of survival.

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Using the Internet to research and respond to their health needs made a real difference in getting access to information about their disease, blogging stories, sharing digital health records or finding expert treatments. Public health systems or private doctors lack the capacity to address all issues of individual patients' needs, and self-help and peer-to-peer emotional support by fellow sufferers are thriving at the crossroads of information technology with health management. The physician, writer and myeloma patient Tom Ferguson, MD coined the term e-patients in 1999 for empowered medical consumers (Ferguson and Frydman 2004). The conceptual framework of the e-patient movement and Participatory Medicine/Health 2.0 (Kabat-Zinn 2000; Silber 2009; Van De Belt et al. 2010) became broadly known with blogging cancer activist Richard Davies de Bronkart Jr ('e-patient Dave'). Today the term e-patient is well established to describe the growing community of internet health seekers in the USA, Europe and Canada, and authors of the online encyclopaedia Wikipedia provide the following definition:

> *An e-patient (also known as Internet patient, or Internet-savvy patient) is a health consumer who uses the Internet to gather information about a medical condition of particular interest to them, and who use[s] electronic communication tools (including Web 2.0 tools) in coping with medical conditions. The term encompasses both those who seek online guidance for their own ailments and the friends and family members (e-Caregivers) who go online on their behalf. e-patients report two effects of their online health research: 'better health information and services, and different (but not always better) relationships with their doctors.'*
>
> *As use of the term e-patient has evolved, there has been less emphasis on Internet access and technology,*

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> *and a contention that the 'e' in 'e-patient' stands for 'empowered, engaged, equipped, enabled'.*
>
> *e-patients are increasingly active in their care and are demonstrating the power of the Participatory Medicine or Health 2.0 / Medicine 2.0 model of care. They are equipped, enabled, empowered, engaged, equals, emancipated and experts.*
>
> (Wikipedia: e-patient)

Current examples of virtual health communities include PatientsLikeMe (*www.patientslikeme.com/*). PatientsLikeMe is currently working together with the AKU Society (*www.alkaptonuria.info/*) to create the first open, global registry for patients with alkaptonuria (AKU, *www.patientslikeme.com/conditions/157-alkaptonuria*). This is one of the world's rarest diseases, estimated to affect one person in every 250 000–500 000 and leads to the condition that causes bones and cartilage to become black and brittle. It was the first genetic disease discovered. Through this collaboration, patients with AKU can now track their disease progression, connect with others who have the disease, and contribute health data to the registry's real-time research platform.

Other examples include RareConnect, a virtual online health community dedicated specifically to rare disease patients. It is a common project of NORD and EURORDIS in existence since 2009. Currently 31 disease-specific communities allow patients to safely meet each other, share experiences and share information such as standards of care, treatment info, etc. with patients globally. Please refer to section 3.4.2 and the RareConnect website (*www.rareconnect.org/en*) for more information.

Further examples of virtual health communities include CureTogether (*http://curetogether.com/*), e-patients.net (*http://e-patients.net/*), Pew Internet and American Life Project

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(*www.facebook.com/pewinternet*) together with a number of Facebook groups as well as numerous Twitter accounts and blogs.

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4

Organisations and networks dedicated to rare diseases and orphan drugs

With additional contributions by Chris Wilson

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Abstract: Rare diseases differ from their more common counterparts in many aspects. This applies as well to the role of national and international organisations and networks. They are a major source of information and point of contact for patients, counsellors to public health decision-makers, coordinators and drivers for the researcher, and funding providers for the drug industry. The most prominent and influential organisations dedicated to and disseminating knowledge of rare diseases and orphan drugs are Orphanet, ICORD, EPPOSI, EGAN and Genetic Alliance.

Key words: organisations, network, Orphanet, ICORD, EPPOSI, EGAN, Genetic Alliance.

Patient network and advocacy groups are major stakeholders within all activities related to rare diseases, with the biggest organisations being EURORDIS in Europe and NORD in the USA (Chapter 3). They organise various events to

increase awareness in the general public and between various policymakers. Rare Disease Day is an annual, awareness-raising event that is coordinated by EURORDIS and NORD. The European Conference on Rare Diseases and Orphan Products (ECRD) is a conference organised by EURORDIS. These initiatives have been discussed in Chapter 2.

This section discusses national and international, governmental and non-governmental organisations and networks that link patient associations, academic researchers, developers in the pharmaceutical industry, healthcare providers, political decision-makers, and other professionals who are dedicated and contributing to the dissemination of knowledge about rare diseases and their treatments.

4.1 Organisations and networks: their roles and activities

The rare and orphan diseases community is characterised by strong public-private collaboration through the involvement of national and international organisations and networks that constitute the majority of stakeholders in this health area, unlike what is observed with more common diseases.

Organisations and networks are frequently the drivers to initiate new research on a specific disease through the securing of private, governmental or international funding, coordinating among patients and caregivers in different geographic areas, and facilitating the dissemination of knowledge about the condition.

Over the last few years, these organisations and networks have played a very complex and crucial role through increasing public awareness, political lobbying, serving as a point of reference and contact, providing expert knowledge on the disease for affected patients, collecting data, setting

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up networks by linking centres, and funding of projects. They have also established very strong collaborations with patient advocacy groups (Chapter 3). The overall goal of these organisations is the streamlining of isolated research and disseminated patients and local activities into a harmonised process. As a result, the efforts to link isolated and fragmented research initiatives through networking have significantly improved the efficiency and total capacity of research related to specific rare diseases and orphan drugs.

4.2 European organisations and networks

4.2.1 Orphanet

Networking in the field of rare diseases is a perceived necessity in Europe (Aymé and Schmidtke 2007). This wisdom has contributed to the creation of Orphanet (*www.orpha.net/*), which is a web portal and public database on rare diseases.

The database was initiated by the National Institute of Health and Medical Research, France (INSERM) and is today maintained by a European consortium of 38 participating countries, coordinated by France. Access both for physicians and patients is free of charge, with English, French, German, Italian, Portuguese and Spanish user interfaces.

Orphanet is governed by various committees: the Steering Committee of representatives from the agencies and bodies that finance Orphanet, the Management Board made up of Orphanet country coordinators, and the International advisory Board consisting of approximately 100 international

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experts. National teams are responsible for the collection of information on specialised clinics, medical laboratories, ongoing research and patient organisations in their country. Partner countries outside of Europe are Armenia, Israel, Lebanon, Morocco, Quebec/Canada and Turkey. Canada joined Orphanet in 2011 and negotiations are ongoing with Argentina, Australia, Brazil, China and Japan to become Member States and hence contribute to the knowledge and expertise available within the organisation. The infrastructure and coordination activities are funded jointly by INSERM, the French Directorate General for Health, and the European Commission. Services are additionally supported by other partners including the Association Française contre les Myopathies / the French Muscular Dystrophy Association (AFM) – Téléthon, LEEM (French Foundation of Drug Manufacturers), Foundation Groupama, LFB Group and GSK.

The web portal offers information packages for patients, professionals, researchers and industry. At the time of writing there are approximately 5950 diseases, 4900 clinical expert centres, 15 000 health professionals and 5400 laboratories registered in the database.

Orphanet provides the following database services:

- an inventory and a classification of rare diseases (including prevalence and cross-referenced genetic information with Human Genome Organisation Gene Nomenclature Committee (HGNC), OMIM[1], with GenAtlas[2] and SwissProt[3]);
- an encyclopaedia of rare diseases (English, French; for patients and professionals);
- an inventory of orphan drugs (all stages of development, from EMA's orphan drug designation to marketing authorisation);

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- a searchable directory of disease-related services (specialised medical facilities (centres of expertise), diagnostic laboratories, research activities, clinical trials, patient registries, advocacy organisations);
- a diagnostics tool (search by signs and symptoms);
- guidelines for emergency medical care and anaesthesia;
- OrphaNews, a bimonthly newsletter (scientific and political information, in English and French) from EUCERD;
- Orphanet Reports Series (e.g. Lists of orphan drugs in Europe, Disease Registries in Europe, Prevalence of diseases).

OrphaNews was launched in 2005 and over 80 issues have been published since, which are sent to over 13 000 current subscribers.

Orphanet provides the opportunity to patient groups to create their own web presentation. After registration in the database, patients may get in contact with organisations of other patients suffering from the same rare disease. A link list of 30 research platforms is also provided (e.g. ERA-Net: E-Rare–2 project; *www.e-rare.eu/*). Orphanet is linked to the network of European Diagnostic Laboratories (EuroGentest; *www.eurogentest.org/*) and to current information on rare diseases by the European Commission (Directorate General Health and Consumers; *http://ec.europa.eu/health/rare_diseases/policy/index_en.htm*). The related Orphadata database (*www.orphadata.org*) gives access to large datasets (e.g. epidemiological data, clinical signs, associated genes) for research purposes of the scientific community.

Orphanet established a scientific partnership with the International Union of Basic and Clinical Pharmacology

(IUPHAR) in 2011 to link diseases with receptor information and drugs. It also cooperates with the European Bioinformatics Institute (EBI) to relate disease information to genomic, protein and biochemical pathway data and contributes to the ongoing revision of the WHO International Classification of Diseases (ICD–11; see Chapter 2).

For further information, the organisation publishes an open-access online journal (*Orphanet Journal of Rare Diseases; www.ojrd.com/*).

4.2.2 European Platform for Patient Organisations, Science and Industry (EPPOSI)

European Platform for Patient Organisations, Science and Industry (EPPOSI; *www.epposi.org*) is a not-for-profit organisation founded in 1994 in Belgium. This international association is dedicated to supporting healthcare policymaking and describes itself as a think tank where members such as patient organisations, drug manufacturers, and academic organisations can interact and exchange information.

The patient organisations included cover a broad spectrum of diseases such as AIDS, incontinence, Parkinson's disease, prostate cancer, mental illness, Crohn's disease or thalassaemia to name only a few. EURORDIS represents the patients with rare diseases within EPPOSI. A total of 18 large pharmaceutical and biotechnology companies and manufacturers of medical devices as well as five industrial associations are members of EPPOSI. Members of scientific organisations include the European Society of Human Genetics, the Amsterdam Lysosome Center, Cancer Research UK, the European Society for Clinical Investigations, the

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Union of European Medical Specialists, the Regulatory Affairs Professionals Society and others.

Currently, EPPOSI is focusing on four research areas through its Advanced Innovation Programmes (AIP):

- chronic conditions management (AIP-CCM)
- health technology assessment (AIP-HTA)
- innovation in healthcare (AIP-INNO)
- rare diseases (AIP-RD).

The key objective of AIP-RD is to build on EPPOSI's long-established work in the rare diseases arena to focus on specific areas where its multistakeholder perspective can complement the actions of existing and new partners in the field.

The progress of EPPOSI programmes proceeds in four steps from research (web surveys, opinion polling, data distillation, scientific papers, outcome measurement), via hypothesis testing/validation (workshops, symposia, discussions, scientific events), generation of consolidated recommendations (white papers, policy briefs, consensus reports) to dissemination of these materials to stakeholders. The wider public is therefore provided with high quality independent research.

Information is spread by newsletters, web surveys, HTA surveys, 'Stakeholder Days' and other events and communicated by email, webinars and expert meetings.

Rare disease activities within EPPOSI are structured as the EPPOSI Rare Diseases Interest Group (RDIG). Its main mandate is to suggest project topics and to address rare disease issues in other programmes. Current projects, as stated in the RDIG 2013 Work Programme, are to address the specificity of Rare Disease Challenges from a multistakeholder perspective on a minimum of two discrete

rare disease policy projects such as the impact of ageing (rare disease patients who go on to develop age-related chronic conditions and how to diagnose and manage these co-morbidities) and neonatal screening.

Key output and events have already been identified for 2013 and will include publishing a White Paper on 'Stakeholder perspectives on the value of systematic neonatal screening programmes in Europe: ethical and cost factors', and conducting studies on 'How to apply a multi-stakeholder approach in Rare Disease policy-making' and on 'Maintaining quality of management of Rare Diseases: a system approach'.

4.2.3 EGAN

EGAN (*www.egan.eu*) is a network of both national genetic alliances and European disease-specific patient organisations with a special interest in medical research in genetics, genomics and biotechnology. Genetic or congenital disorders are represented, both rare and common.

EGAN was founded as a non-profit organisation in 2005 in Brussels and has voluntary staff only. The alliance operates with a secretariat provided by the Dutch Genetic Alliance in the Netherlands. The membership includes national alliances (The Dutch Genetic Alliance, Genetic Alliance UK, Swedish Genetic Alliance), regional alliances (Central and Eastern European Genetic Network, CEEGN), general (Seriously Ill for Medical Research, SIMR) and European disease-specific organisations (covering conditions such as blindness, Crohn's disease, Gaucher's disease, haemophilia, hemiplegia, hereditary ataxias, dystonia, neuromuscular disorder, cancer, dyslexia, epidermolysis bulosa, heart diseases, Pompe's disease). EGAN is represented on the Committee for Orphan Medical Products and the Committee for Advanced Therapies (CAT) of the EMA.

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EGAN is a member of the European Patients' Forum (EPF), EPPOSI, and the International Genetic Alliance (IGA).

EGAN works in various fields related to current issues in genetics and healthcare delivery including gene and cell therapy, biobanks, patient registries, animal experimentation, screening tests, paediatric medicines, and patent protection. EGAN currently participates in European projects including Global Research in Paediatrics (GRIP), the Genetic and Epigenetic Networks in Cognitive Dysfunction (GENCODYS) and the Preparing for Life Initiative. Past projects comprised the EuroGenGuide on patient participation in genetic data and biobanking, GENED which was an educational programme for non-genetics health professionals to improve understanding of genetic testing, and NEPHIRD which established a European network for collection of epidemiological and public health data on rare diseases.

The activity of EGAN is sponsored by national and European governmental institutions (European Commission, The Netherlands Organisation for Health Research and Development), organisations (Genetic Alliance UK, Dutch Genetic Alliance, King Boudewijn Foundation) and the pharmaceutical industry (Genzyme, AMGEN, Novartis, Roche). The organisation actively looks for further donations to support its activities.

EGAN publishes information as part of the IGA newsletter.

4.3 American organisations and networks

4.3.1 Genetic Alliance

Genetic Alliance (*www.geneticalliance.org*) is the largest US non-profit health advocacy organisation, which

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includes in its network more than 1000 disease-specific advocacy organisations, as well as universities, private companies, government agencies, and public policy organisations.

The organisation was founded by social worker Joan O. Weiss in Washington DC in 1986 (originally as the Alliance of Genetic Support Groups). Genetic Alliance wants to improve health through the authentic engagement of communities and individuals to build capacity within the genetics community by creating partnerships between stakeholders, improving information for better decision-making, and facilitating the transfer of basic research into novel health technologies.

Activities and services of Genetic Alliance include an Annual Conference, numerous webinars, creation of entries in WikiGenetics (*http://wikigenetics.org/*) and WikiAdvocacy (*http://wikiadvocacy.org*), participation of the community in the Advocates Partnership Program (waived registration fees to attend the annual conferences of national organisations), maintenance of Disease InfoSearch (*www.diseaseinfosearch.org/*; searchable database with information on advocacy organisations and disease descriptions), Listserv Hosting for advocacy organisations, and assistance in establishing disease-specific groups.

Genetic Alliance has developed a series of programmes designed to increase the visibility of genetics and advocacy, to establish strong networks, and to advance important campaigns. Current programmes include:

- Access to Credible Genetics Resources Network. This programme provides consumers and health professionals with increased access to quality information on Duchenne and Becker Muscular Dystrophy as well as Fragile X syndrome.

- Consumer Focused Newborn Screening Initiatives. This programme is a comprehensive resource on neonatal screening (Baby's First Test) for the public.
- Family Health History Programs. The idea is to develop community-created tools for discussing family health history and translate knowledge into healthy choices.
- Congenital Conditions Program. This programme collects evidence-based information and coordinates supportive care for parents whose child received a diagnosis prenatally, at birth, or up to one year after birth.
- Genetics for Early Disease Detection and Intervention to Improve Health Outcomes. This is an initiative for early disease detection using clinical, genetic, and family health history information.

Genetic Alliance has managed a biobank[4] (Genetic Alliance Registry and BioBank; *www.biobank.org/*) since 2003.

Genetic Alliance further provides an electronic collection of documents, audio, and video files from the community in topic areas such as newborn screening, family health history, genetic testing, reimbursement, research, drug development, community engagement, and organisational development (Resource Repository; *www.resourcerepository.org*).

Several free publications from the Genetic Alliance for patients and professionals are available online:

- *Genetic Testing and Molecular Biomarkers* (peer-reviewed official journal).
- Advocacy in Genetics (e-newsletter).
- Newborn Screening Newsletter (quarterly newsletter).
- Weekly Bulletin (weekly update to our Announcements listserv).

- Policy Bulletin (legislative updates, Congressional and regulatory agency activity, newly-released publications).
- Registry and Biorepository Bulletin (monthly update on biorepositories, relevant funding announcements, training opportunities, scientific meetings).
- How Do I Talk to My Family About My Genetic Condition? (Booklet on how to share a diagnosis of a genetic condition with the family).
- 'Does It Run In the Family?' Toolkit (two booklets and supplementary materials).
- Making Sense of Your Genes: A Guide to Genetic Counselling (consumer-friendly introduction to genetic counselling).
- How-to Guides (practical guides for genetic advocacy).
- Understanding Genetics: A Guide for Patients and Health Professionals (basic genetics concepts, diagnoses of genetic conditions).
- Genetic Alliance Monographs (four monographs: 'Genomics, Cancer Care and Advocacy', 'Genetic Testing Stories', 'Eyes on the Prize: Truth Telling about Genetic Testing', and 'Community Centered Family Health History: How Do You Make Research Community-Specific and Universally-Relevant?').

The activity of Genetic Alliance is mainly funded by federal grants (60%: Maternal and Child Health Bureau, MCHB), government contracts (20%: Centers for Disease Control and Prevention, CDC; NIH / National Library of Medicine, NLM; Health Resources and Services Administration, HRSA) and to a minor degree by fees for service, individual donors, and industry support.

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4.3.2 Rare Diseases Clinical Research Network (RDCRN)

In response to the Rare Diseases Act, the RDCRN (*http://rarediseasesnetwork.epi.usf.edu*) was created in 2003 by the US NIH and the FDA ORDR. Originally ten and since 2009 19 research consortia, each dedicated to studying different diseases, as well as one Data Management Coordinating Center, collaborate within the network.

Funding of the individual clinical research consortia is provided by the following: the National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), National Institute on Aging (NIA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Dental and Craniofacial Research (NIDCR). The goal of these consortia is to facilitate collaboration among experts in many different types of rare diseases, to involve patient groups as active participants and to contribute to the research and treatment of rare diseases (identification of biomarkers, diagnosis, prevention, development of therapies, etc.).

The following Research Consortia are currently active:

- Angelman, Rett, And Prader-Willi Syndromes Consortium
- Autonomic Rare Diseases Clinical Research Consortium
- Brain Vascular Malformation Consortium
- Chronic Graft Versus Host Disease Consortium (CGVHD)

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- Clinical Research Consortium for Spinocerebellar Ataxias
- Dystonia Coalition
- Genetic Disorders of Mucociliary Clearance
- Inherited Neuropathies Consortium
- Lysosomal Disease Network
- NEPTUNE: Nephrotic Syndrome Rare Disease Clinical Research Network
- North American Mitochondrial Diseases Consortium
- Porphyrias Consortium
- Primary Immune Deficiency Treatment Consortium
- Rare Kidney Stone Consortium
- Salivary Gland Carcinomas Consortium
- STAIR: Sterol and Isoprenoid Diseases Consortium
- Urea Cycle Disorders Consortium
- Vasculitis Clinical Research Consortium.

Former partners of the RDCRN are:

- Bone Marrow Failure Consortium (BMFC)
- Cholestatic Liver Disease Consortium (CLiC)
- Clinical Investigation of Neurologic Channelopathies (CINCH)
- Rare Genetic Steroid Disorders Consortium (RGSDC)
- Rare Lung Diseases Consortium (RLDC)
- Rare Thrombotic Diseases Consortium (RTDC).

The Research Consortia provide individual websites (in English, some of them also in Spanish), which contain information for patients and physicians regarding disease information, treatment guidelines, ongoing studies, and contact data for patient registries.

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The RDCRN maintains a listing of ongoing clinical trials, which includes information on the disease under study, study title, recruitment status, a brief study description, eligibility criteria, and contact data or locations of participating hospitals.

A contact registry is maintained to provide an opportunity for individuals with a specific rare disease or disorder to register themselves to receive information about studies conducted by the RDCRN. Patients are invited to join the registry, which is used by clinical researchers to contact individuals who might qualify for participation in a study that otherwise would have difficulty finding enough patients because of the rarity of the conditions. The number of diseases in this patient-reported registry has grown from 42 to 201 since 2007 (Richesson et al. 2012).

Spotlight on Rare Diseases is a quarterly eNewsletter issued by the RDCRN as a single resource for information on the activities and achievements of the RDCRN and an educational tool for members of the rare disease community who are not part of the network.

4.4 International organisations and networks

4.4.1 International Conferences for Rare Diseases and Orphan Drugs (ICORD)

The International Conference on Rare Diseases and Orphan Drugs (ICORD; *http://icord.se*) society is an international organisation for individuals who are active in the field of rare diseases and orphan drugs, with members from academia, industry, patient organisations, regulatory and health authorities, health professionals, and public policy leaders.

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Participants of the 1st ICORD 2005 in Stockholm proposed to create the ICORD Society, which finally was founded in Brussels in 2007. ICORD is financed by annual membership fees.

The ICORD mission is to improve the welfare of patients with rare diseases and their families worldwide through better knowledge, research, care, information, education and awareness. The organisation intends to promote research, ethics, policies and actions on rare diseases and orphan products in all regions of the world, to provide a global forum for all stakeholders for effective communication, to enhance international cooperation, and to develop tools to address common issues in rare diseases and orphan products.

ICORD organises annual international conferences. The last ICORD conference was held in 2012 in Tokyo, Japan and covered research, diagnosis, treatment of rare diseases, orphan drugs, health policies, ethical issues and social aspects of rare diseases, international networking, and patients' needs as main topics.

The International Rare Diseases Research Consortium (IRDiRC) (please also see section 5.4.1)

One of the initiatives promoted by the European Commission, Health Directorate, DG Research and Innovation, and the US NIH ORDR is the IRDiRC. The goals of the consortium are to deliver by 2020, 200 new therapies for rare diseases and diagnostic tests for most rare diseases.

A third workshop run by IRDiRC was held in Montreal, Canada in 2011, following two previous successful workshops held in Iceland and the USA, and involved some 100 international participants (including public and private funding organisations, scientists, regulators, industry, and patient groups).

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One of the aims of the workshop was to develop common scientific and policy frameworks that will guide the activities of the participating IRDiRC members. Identifying priority research areas was a principal topic, as well as addressing the regulatory challenges in an international context, including the need for harmonised regulatory requirements.

4.5 Notes

1. Edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine
2. René Descartes University Paris, Centre of Bioinformatics.
3. Protein sequence databases of the Swiss Institute of Bioinformatics (SIB)
4. A collection of human tissue samples and medical information about donors used for research

4.6 References

Aymé, S. and Schmidtke, J. (2007) 'Networking for rare diseases: a necessity for Europe', *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*, 50(12): 1477–83.

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5

Policies and research funding

With additional contributions by Chris Wilson

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Abstract: With the introduction of orphan drug legislation, the possibility of providing treatments for rare disease patients became reality although the initial legislation has proven to be insufficient. A number of policies have now been initiated at the European level to improve cooperation and information sharing for better patient access to much needed treatments. Funding has been made available in the EU through the European Framework programmes and in the USA through the NIH Therapeutics for Rare and Neglected Diseases (TRND) Program for research in rare diseases. To avoid duplication of regional efforts, an International Rare Diseases Research Consortium (IRDiRC) has been established.

Key words: policies, EUROPLAN, National Plans, Framework Programmes, TRND, IRDiRC.

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5.1 Policies on rare diseases

5.1.1 Rare diseases: what are they?

Life-threatening or chronically debilitating diseases – mostly inherited – that affect so few people that combined efforts are needed to:

- reduce the number of people contracting the diseases;
- prevent newborns and young children dying from them;
- preserve the sufferers' quality of life and socio-economic potential.

To achieve these aims help is needed to ensure that scarce resources that are currently fragmented across countries can be pooled, as this can help both patients and professionals share expertise and information across borders.

To promote this activity and to provide assistance, a number of policies have been formulated at both the national and international level.

In general, the aims of Orphan Drug / Disease Policies are to:

- improve recognition and visibility of rare diseases;
- ensure that rare diseases are adequately coded and traceable in all health information systems (please refer to Chapter 2);
- provide support for national plans for rare diseases;
- strengthen cooperation and coordination;
- create 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;
- encourage more research into rare diseases through various incentives, such as reduced fees or establishing periods of market exclusivity;
- evaluate current screening population practices.

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5.1.2 Legal basis of policy in the USA

To date, four bills have been passed in the USA, which together have established the arena for promoting the research and development of orphan drugs to treat very rare diseases. In 1983 the first of these bills (the Orphan Drug Act) was passed, which was intended to encourage pharmaceutical companies, through various financial incentives, to develop drugs for treating rare diseases. NORD was instrumental in passing this legislation, and it continues to play an active role in lobbying members of Congress and the key administrators of federal agencies (*http://rarediseases.org/about/vision-mission*). However, progress has not been entirely smooth, and in 1990 Congress passed a bill that was intended to limit the market exclusivity offered under the Orphan Drug Act, (an important incentive in developing orphan drugs), but this bill was ultimately vetoed by President Bush, who claimed that such a change could discourage manufacturers from entering the orphan drug market (Villarreal 2001).

More positively, Congress passed the second important bill, the Rare Diseases Act of 2002, which established, by statute, the NIH ORDR. It also established the operating mandate of the ORDR, which includes the promotion of cooperation between the NIH to advance research in the field of rare diseases, as well as to support cooperation with the regional centres of excellence for clinical research into training in, and demonstration of, diagnostic, prevention, control and treatment methods for rare diseases.

In conjunction with this bill, the Rare Diseases Orphan Product Development Act was also passed, which provided further incentives for companies to develop drugs for rare diseases (which have been discussed in detail in Chapter 1).

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The most important incentives are as follows:

- tax credits – up to 50% of qualified clinical trial costs;
- waiver of user fees – $1.8M;
- 7 years of marketing exclusivity.

However, the FDASIA includes possibly the most significant measures for rare disease patients and their families since the Orphan Drug Act of 1983. Drafted for the purpose of reauthorising the PDUFA, this Act includes a number of provisions that significantly impact on rare disease patients.

FDASIA and PDUFA V both elevate the role of patients in developing orphan therapies. They mandate that FDA implement ways to bring patients' views into drug development and FDA's regulatory review. The provisions in PDUFA V relate to:

- accelerated patient access to new medical treatments;
- resolution of conflict-of-interest provisions introduced in the previous PDUFA reauthorisation;
- accelerated development of 'breakthrough therapies' that show early promise;
- enhanced FDA consultation with rare disease medical experts;
- a rare paediatric disease priority review voucher incentive programme;
- the development of HUDs (medical devices for small patient populations).

As referenced above, the PDUFA provides essential funding for the FDA by authorising the agency to charge user fees to companies seeking to have products reviewed. Originally enacted in 1992, it must be reauthorised every 5 years, and the last Act was reauthorised in September 2012.

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In the PDUFA Authorization Performance Goals and Procedures for Fiscal Years 2013–2017, the FDA committed to:

- improving the understanding among FDA reviewers of approaches to studying drugs for rare diseases;
- considering non-traditional clinical development programmes, study design, endpoints and statistical analysis in trials for these drugs and in these diseases;
- recognising particular challenges with post-market studies given the small patient numbers;
- encouraging flexibility and scientific judgement on the part of reviewers when evaluating investigational studies and marketing applications for drugs for rare diseases.

For further information, please see:
www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

By mid-FY 2014, the FDA, through the Rare Disease Program, will conduct a public meeting to discuss clinical trials in this subject, including endpoint selection, use of surrogate endpoints/Accelerated Approval, and clinical significance of primary endpoints, also reasonable safety exposures, assessment of dose selection, and development of patient-reported outcome instruments.

By the end of FY 2015, the FDA will develop and implement staff training related to development, review and approval of drugs for rare diseases.

Finally, by the end of FY 2016, the FDA, through the Rare Disease Program, will develop a tool to evaluate the success of the activities of the Rare Disease Program, including the reviewer training.

Further important Acts in the field of rare disease include:

The TREAT Act

The Transforming the Regulatory Environment to Accelerate Access to Treatments (TREAT) Act (*www.hagan.senate.gov/files/TREAT_ACT_Background.pdf*) includes provisions to expand FDA's Accelerated Approval pathway, address the conflict-of-interest issue, provide greater clarity, consistency and transparency in the review process, and encourage innovation and adoption of modern scientific tools in regulatory science.

The Faster Access to Specialised Treatments (FAST) Act

The Faster Access to Specialised Treatments (FAST) Act (*http://thomas.loc.gov/cgi-bin/query/z?c112:H.R.4132:*) was aimed at accelerating the development of treatments for rare diseases while maintaining the FDA's high standards for safety and efficacy.

The Advancing Breakthrough Therapies for Patients Act

The Advancing Breakthrough Therapies for Patients Act addressed the need to provide expedited development and evaluation of potential therapies that show promise early in the research process.

The EXPERRT Act

Championed by the Cystic Fibrosis Foundation, the Expanding and Promoting Expertise in Review of Rare Treatments (EXPERRT) Act (*www.govtrack.us/congress/bills/112/hr4156*) was designed to expand cooperation between the FDA and outside rare disease experts and patient advocates.

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The Creating Hope Act

This Act would expand a priority review voucher programme to incentivise the development of new drugs for rare paediatric diseases, including childhood cancers.

HUDs – medical devices developed for small patient populations

This programme encourages the development of medical devices for patient populations of fewer than 4000 people. Provisions included in the FDA Safety and Innovation Act are aimed to encourage the development of devices for both paediatric and adult patients and to also expand the existing paediatric device incentive to adult HUDs.

5.1.3 Legal basis of EU policy

The specificities of rare diseases, including a limited number of patients and scarcity of relevant knowledge and expertise, single them out as suitable for addressing at the European level. European cooperation can help to ensure that limited knowledge can be effectively shared and resources combined as efficiently as possible.

The European Commission has already taken important steps in many areas to address the issues of rare diseases, and these will be discussed further.

Key policy documents

At the European level, there are currently three key policy documents establishing a political framework for action in the field of rare diseases and orphan medicinal products:

The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 as previously described in Chapter 1 was

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introduced to set up the criteria for orphan designation in the EU and describes the incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. Although this EU policy significantly stimulated research in this area, Member States do not yet ensure full access to each authorised orphan drug approved (see Chapter 7).

The Commission Communication on Rare Diseases: Europe's Challenge (2008) sets out an overall Community strategy to support Member States in diagnosing, treating and caring for the 36 million EU citizens with rare diseases. The Communication focuses on three main areas:

- improving recognition and visibility of rare diseases;
- supporting policies on rare diseases in the Member States for a coherent overall strategy;
- promoting cooperation, coordination and regulation for rare diseases at the EU level.

This Communication was also instrumental in producing the Council Recommendation on an action in the field of rare diseases (2009). This Recommendation concentrates on supporting and strengthening the adoption, before the end of 2013, of national plans and strategies for responding to rare diseases, on improving recognition and visibility of rare diseases, on encouraging more research into rare diseases, and forging links between centres of expertise and professionals in different countries, through the creation of ERNs in order to share knowledge and expertise and, where necessary, to identify where patients should go when such expertise cannot be made available to them. The role of patients' organisations is also highlighted as particularly important.

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The seven key themes of the Council Recommendation are:

- *Plans and strategies in the field of rare diseases* – calls on the Member States to elaborate and adopt a plan or strategy by the end of 2013 (see EUROPLAN link at the end of this list). The following actions have been identified and agreed: a) assessment of the patients' needs and health system resources, b) creation of a mechanism supporting the national plan or strategy, c) draft a plan or strategy, d) identification of initiatives and actions, e) ensure sustainability, f) monitor the implementation, evaluate the results and revise the plan accordingly and devising and putting in place a mechanism of governance with the involvement of different stakeholders.
- *Adequate definition, codification and inventorying of rare diseases* – brings up the common definition of a rare disease as a condition affecting no more than 5 per 10 000 persons; aims to ensure that rare diseases are adequately coded and traceable in all health information systems based on the World Health Organization's International Classification of Disease and in respect of national procedures; encourages Member States to contribute actively to the inventory of rare diseases based on the Orphanet network.
- *Research on rare diseases* – calls for the identification and fostering of rare disease research at all levels.
- *Centres of expertise and ERNs for rare diseases* – asks the Member States to identify and facilitate networks of expertise based on a multidisciplinary approach to care, and foster the diffusion and mobility of expertise and knowledge.
- *Gathering the expertise on rare diseases at a European level* – calls on Member States to share best practices, develop medical training relevant to the diagnosis and management of rare diseases, coordinate European

guidelines, and, to minimise the delay in access to orphan drugs, to share clinical/therapeutic added-value assessment reports at the Community level.

- *Empowerment of patient organisations* – calls on Member States to consult patient representatives on policy development, facilitate patient access to updated information on rare diseases, and promote patient organisation activities.
- *Sustainability* – highlights that long-term sustainability in the field of information, research and healthcare of infrastructures must be ensured.

For further information, please see:
http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/2_EUROPLAN_Recommendations_for_Rare_Disease_National_Plans_Final.pdf

To promote cooperation and communication as identified in this Commission Communication, the European CAVOMP (see also Chapter 7) study was initiated. This study aims to set up a mechanism for the exchange of knowledge between the Member States and European Authorities in order to facilitate Member States' informed decision on the scientific assessment of the clinical effectiveness of an orphan drug, also known as a HTA, without creating any new regulatory hurdles. This is an assessment conducted post-marketing approval to examine the utility and 'cost-effectiveness' of the proposed treatment, and is critical, particularly in the field of orphan drugs, in determining whether a drug may be reimbursable.

Definitions of HTA

- HTA considers the effectiveness, appropriateness and cost of technologies. It does this by asking four fundamental questions: Does the technology work, for whom, at what

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cost, and how does it compare with alternatives? (UK National Health Service R&D Health Technology Assessment Programme 2003).

- HTA '. . . is a structured analysis of a health technology, a set of related technologies, or a technology-related issue that is performed for the purpose of providing input to a policy decision' (US Congress, Office of Technology Assessment 1994).
- HTA describes the technology and its use, which technology is clinically effective, for whom, how it compares with current treatments, (and) at what cost (Canadian Coordinating Office for Health Technology Assessment, 2002).
- HTA is a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology (International Network of Agencies for Health Technology Assessment 2002).
- HTA is 'the systematic evaluation of properties, effects, and/or impacts of healthcare technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in healthcare. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods' (International Network of Agencies for Health Technology Assessment, 2012).
- HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value (EUnetHTA 2012).

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Some further definitions of HTA are given below and further information can be found in Chapter 7.

EU bodies participating in the CAVOMP study include the European Commission, the EMA and its committees: the COMP, the CAT, the CHMP, the PDCO, together with the Pharmaceutical Forum, patients' organisations such as EURORDIS, and the pharmaceutical industry. The central role of the CAVOMP process is to:

- exchange information on rare diseases and drugs;
- develop methodology and tools for scientific HTA adapted for orphan drugs;
- proceed to the product assessments (CAVOMP compilation report at the time of the Marketing Authorisation and CAVOMP relative effectiveness assessment report after a few years following the product launch) according to drug life cycle;
- organise continuous evidence collection for orphan medicinal products as post-marketing activities.

A secondary role of the CAVOMP process is to act as a 'knowledge centre' and proposed to collect all possible information on orphan diseases and healthcare solutions, contribute to developing a continuum between pre-marketing (EMA) and post-marketing (HTA bodies) authorisations and practices and, finally, be the first operational implementation phase of a process delivering at the EU level relative effectiveness assessments dedicated to rare diseases.

A four-step approach within an 'à la carte system' has been proposed in order to better fit with the needs of the different national authorities involved in the HTA processes, including:

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- an 'information exchange' primary activity supporting Member States in giving them the opportunity to access the most complete information on the orphan drug, the targeted pathology, the epidemiology;
- a 'methodology/toolkit dedicated to orphan drug' secondary activity supporting Member States in giving a methodological support specific to the orphan drug in order to run their own assessment;
- an 'analysis' activity proposing reports focused on relative effectiveness to Member States that do not have the time and/or resources to run their own assessment and report;
- and an 'additional evidence generation' activity proposing recommendations for post-marketing evidence generation addressing uncertainties based on national and European shared views.

The CAVOMP initiative is one of many initiatives in the field of rare disease and of health technology assessment. Ten of them are particularly pertinent for CAVOMP to interact with, and they are described below.

EUnetHTA Joint Action on HTA (2010–2012)

This 2-year project relies on the EUnetHTA collaboration, which involves 24 Member States. The objectives are to further develop the 'core HTA' methods, to develop specific methods on Relative Effectiveness (RE) assessment of pharmaceuticals, to set up an information management system, and establish a policy on stakeholders' involvement. As part of this initiative, further discussion will be necessary to determine how the EPAR could make a better contribution to the assessment of relative effectiveness by health technology assessment bodies in the EU Member States.

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The European Union Committee of Experts on Rare Diseases (EUCERD)

EUCERD is charged with aiding the European Commission with the preparation and implementation of Community activities in the field of rare diseases, in cooperation and consultation with the specialised bodies in Member States, the relevant European authorities in the fields of research and public health action and other relevant stakeholders acting in the field. The EUCERD will foster exchanges of relevant experiences, policies and practices between these parties.

EuroScan

EuroScan is a collaborative network of member agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes and settings in healthcare. The long-term aim of EuroScan is to support collaboration through the exchange of information on new and emerging health technologies, share methodologies, and disseminate information on early identification and assessment activities.

Swedish EU Presidency Assessing Drug Effectiveness Project (SPADE)

A meeting was organised on 28–29 July 2009 on the subject of 'Assessing Drug Effectiveness – Common Opportunities and Challenges for Europe' to discuss post-marketing assessment harmonisation and cooperation for the collection and sharing of data on drug effectiveness and safety following marketing authorisation. This meeting led to a pilot project for structured follow-up of the initial testing of an orphan drug, which is the type of medicine requiring the most important effort on collaboration in data collection.

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Tapestry network – Pilots of multistakeholder consultations in early-stage drug development

This project involves the EMA, HTA bodies, payers, pharmaceutical companies, patient associations and clinicians from six Member States (France, Germany, Italy, the Netherlands, Sweden and the UK). The objectives are to propose a non-binding alignment on the evidence required from pharmaceutical companies to demonstrate therapeutic value in phase III clinical studies.

Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) deals mainly with evaluation and recommendation regarding the periodic safety update reports (PSUR), the post-authorisation safety studies (PASS) and the risk management plan (RMP). It is thought that there might be possible synergies on new evidence generation to be made between the HTA cooperation and the EMA's PRAC.

EUROPLAN

The objectives of EUROPLAN are to establish recommendations for the development of Rare Disease national plans by Member States. Its role is also to collect and disseminate best practices, to support national initiatives and to develop indicators for monitoring the implementation and evaluation of national plans.

Centres of Expertise for Rare Diseases and European Reference Networks (ERN)

This initiative is a mapping exercise with a network building objective. After the identification of all existing

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centres/network/association with expertise in a specific rare disease, the initiative will analyse how such European Networks of Centres of Expertise should be built.

Orphanet (for additional information, please refer to section 4.2.1)

Orphanet is the database of reference information on rare diseases and orphan drugs. It provides an encyclopaedia of Rare Diseases, information on orphan drugs, a directory with all centres of expertise, clinical laboratories, research projects, registries, clinical trials and patient organisations related to rare diseases.

EUROPLAN (*www.europlanproject.eu/_newsite_986987/index.html*)

The European Commission had also funded EUROPLAN, a 3-year project that began in April 2008. The main goal of the project was to provide National Health Authorities with supporting tools for the development and implementation of National Plans and Strategies for rare diseases as recommended by the European Council. The supporting tools are composed of three documents focused on defined priority areas: a Guidance document on recommendations for the definition and implementation of National Plans and Strategies for rare diseases, a joint report with the Rare Disease Task Force on initiatives and incentives in the field of rare diseases in Europe, and a document on the recommended set of indicators for monitoring and evaluating the implementation of national initiatives.

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Healthcare Industries Platform on access to medicines in Europe

One further example at the European level is the platform on access to medicines. This is one of the three work areas of the Process on Corporate Responsibility in the field of Pharmaceuticals. The platform is dedicated to enhancing collaboration among the Member States and relevant stakeholders in order to find common, non-regulatory approaches to timely and equitable access to medicines after their marketing authorisation. The members of the platform are all invited to contribute to five projects. Each project is then chaired by the Commission with the support of one Member State. While each project has a balanced representation of Member States, industry and other relevant stakeholders, the composition differs between projects, reflecting their distinctive nature and the different issues they address.

Of relevance to orphan drugs, the following projects have been launched:

Mechanism of coordinated access to orphan medicinal products (MOCA)

Members are invited to develop the concept of a coordinated access to orphan medicinal products based on the set up of programmes between companies and groups of competent authorities and results of the ongoing project on a mechanism for clinical added value on orphan medicinal products. This is part of a wider European Commission initiative on access to medicines and corporate responsibility, and builds on a Belgian project to improve access to orphan drugs. MOCA seeks to reduce disparities in market access to orphan medicines across Member States and additionally supports improved access for

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patients to orphan medicines. The initiative also promotes and supports data sharing and HTA expertise between currently 11 Member States, although there is nothing preventing the remaining Member States from joining.

Capacity building on managed entry agreements for innovative medicines

The objective is to clarify the various approaches to managed entry agreements (also referred to as risk-sharing, outcome-based or performance-based agreements) ensuring access to innovative medicines, including orphan drugs. Based on the initial mapping, members could pursue the exercise by developing further exchanges of practices and knowledge sharing.

Facilitating supply in small countries

The objective is to clarify the specific non-regulatory bottlenecks for the access of medicines in small markets with all concerned parties with a view to defining possibly specific approaches on pricing and reimbursement of medicines in these countries.

EU Directive Cross-Border Healthcare

Finally, the Directive on cross-border healthcare was approved by the European Council (2011), which will establish a legal base for the ERNs of Rare Diseases. The aim of this Directive is to facilitate access to safe and high-quality cross-border healthcare and to promote cooperation on healthcare between Member States, the latter being particularly important in the field of rare disease, where the Commission will have to support Member States in cooperating in the areas of diagnosis and treatment capacity. The EU Member States now have 30 months (from February 2011) to transpose the Directive's provision into national legislation.

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5.1.4 Political framework at Member State level

At the Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. Only a few Member States have currently adopted a national plan/strategy for rare diseases: France, Portugal, Greece, Bulgaria, Spain and the Czech Republic. These plans/strategies vary in their scope and also their financing, which will ultimately influence the extent of their impact at national level.

One of the latest countries to publish a plan for rare diseases is the UK, published in March 2012. This plan calls for the use of specialist centres to make exact diagnoses to make sure people are treated earlier – as in some cases this could save lives. It also states that all doctors should have the right training to be aware of the possibility of a rare disease, and calls for patients' care to be better coordinated, in order to save time, money and inconvenience.

5.1.5 Political framework in other world regions

Outside of the European region, a number of countries have developed political frameworks in the field of rare diseases. Mostly, these initiatives concern the regulation of orphan drugs. As has already been seen, policies for orphan drugs started as early as 1983 in the USA with the adoption of the Orphan Drug Act, and then in Japan and Australia in 1993 and 1997, respectively (see Chapter 1). This list will continue to grow, and it is interesting for example to see that although there is currently no clear definition of orphan drug in China, the orphan drug designation in the USA or EU can now be used as a reference.

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5.2 Research funding in the European Union (EU)

5.2.1 National rare disease research programmes

Very few countries have specific funding programmes for research in the field of rare diseases. Amongst the countries that currently, or previously, have established specific rare disease funding programmes/calls are France, Germany, Hungary, Italy, the Netherlands, Portugal and Spain, as well as Switzerland as a non-EU member.

Many other countries fund rare disease projects through generalised research funding programmes. A few countries (such as France, Italy, the Netherlands and Spain) also have, or have had, specific initiatives and incentives in place to boost research and development in the field of orphan medicinal products at a national level, although this situation is constantly being reviewed, given the impact of cost.

In addition, 'Telethon' initiatives provide funding for rare diseases projects in countries such as Cyprus, France, Italy, Luxembourg, Spain and Switzerland, and in many other countries, disease-specific charities raise funds for research.

5.2.2 Programmes at the European level led by the European Commission Directorate General Research and Innovation

At the European level, research on rare diseases is being addressed as one of the priority areas in the health field under the EU Framework Programmes for Research and Technological Development, which was established in the early 1990s.

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During the Fifth Framework Programme for Research (FP5: 1998–2002) the thematic programme 'Improving the quality of life and management of living resources' included, amongst other topics, fundamental and clinical research in the field of rare diseases. Support was provided for multinational research into rare diseases, applying advances in modern technology to diagnosis, treatment, prevention and surveillance through epidemiology. Forty-seven projects were funded for about €64 million in total.

Under the subsequent Sixth Framework Programme for Research (FP6: 2002–2006), one of the seven thematic areas supported projects focusing on 'Life sciences, genomics and biotechnology for health'. This thematic area stimulated and sustained multidisciplinary research to exploit the full potential of genome information to underpin applications to human health. In the field of applications, the emphasis was on research aimed at bringing basic knowledge through to the application stage (translational approach), to allow real, consistent and coordinated medical progress at the European level and to improve the quality of life. This thematic area was two-fold, one of the aspects being the fight against major diseases, including rare diseases.

FP6 saw a significant increase in the funding for rare disease projects: around €230 million for a total of 59 projects, also including an ERA-Net project (E-Rare).

E-Rare is now a FP7 (Seventh Framework Programme of the European Union for research) funded ERA-Net programme for research on rare diseases. It aims to promote the cooperation and coordination of research activities carried out at a national or regional level in the Member States and Associated States through the networking of research activities conducted at a national or regional level, and the mutual opening of national and regional research programmes.

The aim of the scheme is to help develop a European Research Area by improving the coherence and coordination across Europe of such research programmes. The scheme will also enable national systems to take on tasks collectively that they would not have been able to tackle independently, but at the same time to allow for the different way that research is organised in different Member States and Associated States.

The project now has 16 partners from 12 countries: Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and Turkey.

In the first phase of the project (2006–2010) E-Rare launched two Joint Transnational Calls (JTC). The aim of the first Call was to enable scientists in different countries to build an effective collaboration on a common research project based on complementarities and sharing of expertise. Six E-Rare partnering countries joined the first call in 2007 (France, Germany, Italy, Israel, Spain and Turkey). These National Institutions funded multilateral transnational research projects on rare diseases.

The partners of E-Rare, ERA-Network for research programmes on rare diseases, launched the second JTC at the end of 2008/beginning of 2009. The ten countries that joined the second Transnational Call were France, Germany, Israel, Spain, Turkey, the Netherlands, Portugal, Italy, Austria and Greece; four additional funding organisations from four Member States joined the second JTC. The financial input of each partner research funding agency/ministry provided the funding for 16 transnational research consortia with 75 participating research teams from 10 countries for a total research budget of €9.6 million.

A new E-Rare project (E-Rare–2) (2010–2014) aims to deepen and extend the cooperation established by the first project. At the end of 2010, E-Rare–2 launched its third JTC

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for proposals. Research groups from nine countries (Austria, Belgium, France, Germany, Greece, Israel, Italy, Spain and Turkey) were eligible to participate in this call that seeks to promote transnational research collaboration on rare diseases. Overall, this initiative has allowed for the mobilisation of researchers to tackle the fragmentation of research and the production of new knowledge, encouraging a better coordination of research at the EU level, and fostering dialogue with all stakeholders, including, and importantly, patients.

In the Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7: 2007–2013), rare disease research specifically features under the heading of the Health theme, one of ten themes proposed under the specific programme on 'Cooperation'. This specific programme is designed to gain or strengthen leadership in key scientific and technological areas by supporting transnational cooperation between universities, industry, research centres, public authorities and stakeholders across the EU and the rest of the world.

The European Commission has already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. The rare disease areas of the chosen projects include haematology, metabolic diseases, neurology, dermatology and congenital malformations. Therapeutic approaches include pluripotent stem cells, gene therapy vectors and customised animal models.

For the period 2007–2010, 50 research projects with an EU contribution of over €237 million are being supported, and the Commission has promised a further €100 million for rare diseases in the FP7 Health call in 2012. Rare diseases will therefore continue to be a priority in the next research programme, Horizon 2020, which runs from 2014–2020. This will ultimately lead to better diagnostic methods, new

treatments, better care and prevention strategies for rare diseases. Of the current projects, 17 are specifically devoted to support research on the natural history and the pathophysiology of rare diseases (for a total of €71 million), and 8 projects cover the pre-clinical and clinical development of orphan drugs (for a total of €36 million).

A full list of projects concerning rare diseases supported by the Framework Programmes is available in the Orphanet Report Series ('European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases and European clinical networks funded by DG SANCO and contributing to clinical research in the field of rare diseases'). The list is available on the Internet: *http://cordis.europa.eu/fp7/home_en.html*. It contains projects that have been funded thanks to specific calls on rare diseases and also projects on rare diseases that have been funded through non-specific calls. For example, RareDiseasePlatform (RDPlatform) is a 3-year support action project of the EU's Seventh Framework Programme (HEALTH-F2–2008–201230), which was initiated in May 2008.

The main goal is to create a set of tools for European researchers working in the field of rare diseases, intended to facilitate collaborations between academic teams, SMEs and major companies, and to facilitate access to technological expertise and key research resources. These tools will help the experts, researchers and companies to identify each other and to work together with the ultimate goal of providing diagnostic tools and medical products as quickly as possible. The information collected and disseminated during the development of this project will provide funding agencies with a clear view of what is currently funded at the national and international levels, which could be used as a foundation to target future calls for proposals.

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RDPlatform is an international initiative bringing together organisations from 13 European countries. It was conceived to address unmet needs of the European rare disease research community that were identified during a previous project, the FP6 OrphanPlatform project.

The expected output of the RDPlatform project is:

- to facilitate potential partnerships between research teams, between academic researchers and SMEs, between SMEs, between investment funds and SMEs and even between SMEs and larger private companies;
- to significantly contribute to the market transfer of innovative therapeutics, medical devices and diagnostic tools;
- to accelerate the research process on rare diseases by providing information to the rare disease research community on: databases, biobanks, patient registries, technology platforms and academic and industrial know-how;
- to give value to existing technology platforms, databases and biobanks by facilitating identification of their facilities;
- to provide decision-makers and the community with a clear view of what is currently funded at the national and international levels in the field of rare disease;
- to provide a tool for business intelligence in the field of diagnostic tools, medical devices and orphan medicinal products for rare disease.

The RDPlatform project analysed the data collected by Orphanet and carried out a review of the relevant literature to establish a state of the art of the research activities in the field of rare diseases in order to propose areas for action in the future. They estimate that there are 3880 research

projects for 2100 rare diseases in 27 countries. These projects have been classified as outlined in Table 5.1.

The 'basic research' category gathers research projects such as gene search, mutation search, gene expression profile, genotype–phenotype correlation, in vitro functional study, animal model and human physio-pathological studies. 'Pre-clinical research' covers areas of drug development, gene therapy, cell therapy and medical device development. This research is often performed by the pharmaceutical industry and thus data are not fully accessible, which can explain the low number of projects in the table above. The category 'clinical research' includes non-therapeutic clinical research, epidemiological research but excludes clinical trials. 'Diagnostic and biomarkers' concerns studies that are conducted with the goal of identifying biomarkers and/or of developing diagnostic tests that are not already available in clinical laboratories.

The category represented the most is 'basic research', which is a highly active field representing many challenges and considerable consequences as the outcomes concern both rare and common diseases, with rare diseases often being used as the model for more common disorders.

Table 5.1 State of research in Europe according to Orphanet data

Stage of research	Number of projects
Basic research	2750
Pre-clinical research	331
Clinical research	487
Diagnostic and Biomarkers	312

Source: Aymé and Hivert (2011) p. 41.

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In terms of research and development, orphan designations act as a proxy when considering potential products in development. According to an analysis carried out by Orphanet (*www.orpha.net*), there are 581 orphan designations to potentially treat 343 diseases, affecting a total of 8.2 million people in Europe. This analysis of the Orphanet database also shows that there are 666 ongoing, unique clinical trials for potentially 312 rare diseases. There are 99 marketed drugs for the treatment of 141 diseases. There are 62 drugs with EU market authorisation and orphan designation for 82 diseases, and 44 drugs with market authorisation but without orphan designation for 74 diseases.

In terms of research and development activities by medical domain, an analysis of the number of medical products in development, or with Marketing Authorisation, shows that the greatest number of products has been developed for the treatment of solid tumours, followed by neurology, haematology, metabolism, dermatology and endocrinology.

5.3 Research funding in the USA

Two US institutions are responsible for providing and/or administering research funding to stimulate and support the development of orphan drugs in the field of rare diseases: the FDA and the US NIH.

5.3.1 The FDA Office of Orphan Products Development (OOPD)

The mission of the FDA OOPD is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. In fulfilling

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that task, the OOPD evaluates scientific and clinical data submissions from sponsors to identify and designate products as promising for rare disease and to further advance scientific development of such promising medical products. The Office also works on rare disease issues with the medical and research communities, professional organisations, academia, governmental agencies, industry, and rare disease patient groups.

To fulfil its mission, the OOPD provides incentives for sponsors to develop products for rare diseases. The programme has successfully enabled the development and marketing of more than 350 drugs and biologic products for rare diseases since 1983.

The Orphan Drug Designation programme provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200 000 people in the USA or that affect more than 200 000 persons but are not expected to recover the costs of developing and marketing a treatment drug.

The HUD programme designates a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals in the USA per year as per Federal Regulation 21 CFR 814.3(n).

Grants and other public support programmes are efficient ways to reduce the financial risk associated with research and development of an orphan drug.

The OOPD administers two extramural grants programmes:

- The Orphan Products Grants Program provides funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions. This programme has been used to bring 45 products to market.

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- The Paediatric Device Consortia (PDC) Grant Program provides funding to develop non-profit consortia to facilitate paediatric medical device development, and this has been the first step in the approval of at least 50 Humanitarian Device Exemption approvals.

5.3.2 The Rare Disease Repurposing Database (RDRD)

The FDA's OOPD has established a valuable resource for drug developers, a database of products that:

- have received orphan status designation (i.e. they have been found 'promising' for treating a rare disease) AND
- are already market-approved for the treatment of some other diseases up through June 2010.

While the data included in the Rare Disease Repurposing Database (RDRD) are a re-configuration/cross-indexing of information already released by the FDA, they offer sponsors a useful tool for finding special opportunities to develop niche therapies that are already well advanced through development. For example, these drugs have already been subjected to pre-clinical (e.g. pharmacokinetic and toxicological) testing and are already deemed to be pharmacologically active, effective and safe in some clinical context.

The opportunities tabulated in the RDRD thus represent a far easier starting point for drug developers than beginning with an untested new therapeutic compound.

5.3.3 Rare Diseases Program

This programme run by the FDA aims to facilitate and support the research, development, regulation and approval of drug and biologic products for the treatment of rare disorders.

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Apart from coordinating the development of the Center for Drug Evaluation and Research (CDER) policy, procedures and training for the review and approval of treatments for rare diseases, the programme promotes outside development and maintenance of good science for rare diseases.

In addition the programme will work collaboratively with external and internal rare disease stakeholders to support the development of treatments for rare disorders, and it also serves as CDER's focal point for the rare disease drug development community.

5.3.4 National Institutes of Health (NIH)

The NIH is the US medical research agency. It includes 27 institutes and centres and is a component of the US Department of Health and Human Services. The NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, including investigating the causes, treatments and cures for both common and rare diseases.

Of particular relevance in encouraging the speed and development of new drugs for rare and neglected diseases, the NIH Therapeutics for Rare and Neglected Diseases (TRND) programme was launched in 2009. This unique programme creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists, non-profit organisations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses.

The TRND programme provides an opportunity to partner with and gain access to rare and neglected disease drug development capabilities, expertise, and clinical/regulatory resources in a collaborative environment, with the goal of

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moving promising therapeutics into human clinical trials. TRND uses a solicitation application and evaluation process to select collaborators. If the drug originator applicant is selected, the applicant's team will partner with TRND staff to mutually agree on a joint project plan and to implement the drug development programme. The applicant investigators provide the drug project starting points and ongoing biological/disease expertise throughout the project.

The TRND programme was initially funded through assessments assembled from the budgets of some of NIH's institutes and centres, but now TRND is to be financed directly as part of the National Center for Advancing Translational Sciences' (NCATS) division of pre-clinical innovation (see below).

TRND Projects

TRND doesn't fund projects directly but helps academic and industry organisations access drug development capabilities that include high-throughput screening, medicinal chemistry, and toxicology. At the time of writing TRND has approved 14 projects overall, not including a schistosomiasis collaboration with Rush University that was halted after it failed to achieve milestones.

Two TRND projects, one on sickle cell disease (SCD) and the other on chronic lymphocytic leukaemia (CLL), have advanced to clinical trials: the only drug approved for SCD is the anticancer agent hydroxyurea, which is currently approved for adults only, is of modest efficacy, and has undesirable side effects.

For the CLL project, TRND joined with Kansas University's Institute for Advancing Medical Innovation, the Leukemia and Lymphoma Society (LLS) and the haematology branch

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within NIH's National Heart, Lung and Blood Institute to form The Learning Collaborative. The consortium is repurposing auranofin for relapsed CLL.

Pending final data packages, two other TRND projects could advance to clinical evaluation. One is the development of a therapy for Niemann-Pick type C1 (NPC1) disease, for which there are currently no FDA-approved therapies. The other project is the development of DEX-M74 (ManNAc) as a treatment for HIBM, an adult-onset neuromuscular disorder for which no cure exists.

It is of note that at least half of the projects that are progressing are with small companies looking to collaborate with researchers within the NIH, joined sometimes by investigators from outside the NIH.

Patient groups represent another category of potential partners in rare disease development, an example of which is the involvement of the Parent Project Muscular Dystrophy (PPMD), as two of TRND's projects currently focus on muscular dystrophy, one of which has attracted funding partners that include Congressionally Directed Medical Research Programs.

The future of TRND and just how much it will benefit orphan drug development is linked to the evolution of the NCATS (see below). As the new centre tries to justify itself, TRND could serve to validate the NCATS' focus on translational medicine. It is thought this focus will probably increase as a priority for the NIH, no matter what the next few years hold for the agency in terms of congressional support.

Finally, one further key benefit of TRND could be the forging of closer ties between the traditionally very separate cultures of the NIH and the FDA when it comes to rare disease drug development, although one prerequisite of the programme must be to ensure there is adequate funding for

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the required research and development work on orphan diseases.

National Center for Advancing Translational Sciences (NCATS)

In a move to re-engineer the process of translating scientific discoveries into new drugs, diagnostics and devices by reducing, removing or by-passing the time-consuming bottlenecks that exist in the translational pipeline, the NIH established the NCATS.

The mission of the NCATS is to catalyse the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of indications.

The Centre will not be a drug development company, but will focus on using science to create powerful new tools and technologies that can be adopted widely by translational researchers in all sectors. Working closely with partners in the regulatory, academic, non-profit and private sectors, the NCATS will strive to identify and overcome hurdles that slow the development of effective treatments and cures.

A prime example of the type of innovative projects that will be led by the NCATS is the new initiative between the NIH, the Defence Advanced Research Projects Agency and the US Food and Drug Administration to develop cutting-edge chip technology. This new technology will allow researchers to screen for safe and effective drugs far more swiftly and efficiently than current methods. A great deal of time and money can thus be saved by testing drug safety and effectiveness much earlier in the process.

To meet the goals of the NCATS, the NIH is reorganising a wide range of pre-clinical and clinical translational science capabilities within the NIH into an integrated scientific enterprise.

The following programmes are operating through the NCATS:

- Bridging Interventional Development Gaps, which makes available critical resources needed for the development of new therapeutic agents;
- Clinical and Translational Science Awards, which fund a national consortium of medical research institutions working together to improve the way clinical and translational research is conducted nationwide;
- Cures Acceleration Network, which enables the NCATS to fund research in new and innovative ways;
- FDA-NIH Regulatory Science, which is an interagency partnership that aims to accelerate the development and use of better tools, standards and approaches for developing and evaluating diagnostic and therapeutic products;
- Office of Rare Diseases Research, which coordinates and supports rare diseases research;
- Components of the Molecular Libraries, which is an initiative that provides researchers with access to the large-scale screening capacity necessary to identify compounds that can be used as chemical probes to validate new therapeutic targets;
- TRND, which is a programme to encourage and speed the development of new drugs for rare and neglected diseases (as mentioned above).

The budget for the NCATS is primarily a reallocation of funds from programmes previously located in the NIH Office of the Director, the National Human Genome Research Institute, and the National Center for Research Resources. The NIH is committed to both basic and applied research

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and has maintained a relatively stable ratio of funding across these two areas of focus.

Further information on impetus and development of these programmes is available on the NCATS website.

5.4 Collaborative activities and joint funding

5.4.1 The International Rare Diseases Research Consortium (IRDiRC)

As has already been seen, maximising scarce resources and coordinating research efforts are key elements for success in the rare diseases field, as are well-harmonised regulatory requirements. Worldwide sharing of information, data and samples to boost research is currently hampered by the absence of an exhaustive rare disease classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements.

IRDiRC was set up by the European Commission and the US NIH in 2011 to foster international collaboration in rare diseases research. The IRDiRC will provide a scientific and policy framework to 'guide research activities and foster collaboration among stakeholders to systematically explore all the opportunities to accelerate the development of diagnostics and therapies for rare diseases' (*www.bioendeavor.net/BDDirectory_2658.asp?itemId=10864&countryCode=CA*). The Consortium will ensure fair sharing of the workload amongst countries and avoid funding overlap but will not fund research as such.

It brings together regulatory agencies, researchers, patient group representatives, members of the biopharmaceutical industry, and health professionals and is modelled on similar

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projects, such as the International Cancer Genome Consortium and the International Knockout Mouse Consortium, in which national public funding agencies have set out research roadmaps and funded joint programmes to reach specific objectives as quickly as possible, without any duplication of effort. Each agency issues calls according to its own rules, to meet the shared objectives.

At present, the following governmental funding agencies have officially joined the Consortium: the European Commission, the NIH (US), the Canadian Institute of Health Research (Canada), the National Research Agency INSERM (France), the Federal Ministry of Education and Research (Germany), the National Institute of Health Carlos III (Spain), the Organisation for Health Research and Development (the Netherlands), and the National Institute for Health Research (UK). Also, AFM and Telethon Italia, non-governmental funding agencies, have joined as full members.

The IRDiRC will network the world's top scientists around the shared R&D programme. This large and coordinated effort will aim to understand the patho-physiology of rare diseases, conduct genomic analyses, develop disease models for use in drug discovery and development, look for biomarkers of disease and response to treatment, and support patient registries and related biobanks.

One of the admirable aims of the IRDiRC includes having 200 new treatments for rare diseases available by the year 2020, despite the long timescales involved in drug development. This is thought to be achievable, however, as emphasis will be on repurposing products that are already on the market for treating other diseases. There will of course need to be model agreements in place to permit this, and one of the biggest challenges still outstanding is expected to be intellectual property rights.

A second objective of developing diagnostics for most of the 8000 known rare diseases is another massive challenge, although faster genome sequencing is now making this far easier to achieve. Although it may seem somewhat pointless having a diagnostic for a disease for which there is currently no treatment, for many patients just having a diagnosis is beneficial, as they can connect with other sufferers and learn how to live with the disease. It also allows researchers to gather valuable information about disease progression, which is of great value when looking at possible treatments.

To meet these goals a great deal of collaborative activity must occur:

- to establish and provide access to harmonised data and samples;
- to perform the molecular and clinical characterisation of rare diseases;
- to boost translational, pre-clinical and clinical research;
- to streamline ethical and regulatory procedures.

In addition, IRDiRC will build a critical mass of investigators and clinicians, improving care and increasing well being. The consortium has already attracted industry, academics, governments, regulators and patient advocacy groups, and three workshops have already been successfully run: the first in Reykjavik, Iceland and the second in Bethesda, USA. The most recent workshop was hosted by the Canadian Institutes for Health Research and Genome Canada and was coorganised with the European Commission and the US NIH. The workshops enable participants to share information more widely, identify existing research and development programmes, establish contact with research consortia, networks and biobanks and develop links with the global rare diseases community.

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The first IRDiRC conference was held in Dublin, Ireland, on 16–17 April 2013. It was organised by the European Commission. The conference aimed to gather stakeholders active in the rare disease arena from across the globe. In addition to a top-level programme taking stock of advances toward IRDiRC goals, it provided ample opportunities to network with the international rare disease community. For further information, please visit: *http://jk-events.com/IRDiRC2013/*

5.4.2 International Networking Project

Looking further afield than the USA and the EU, Japan not only has its own well-developed orphan drug programme, but it is also involved in an International Networking Project. The aims of this project are:

- to act as a bridge between Japanese patients with rare diseases and international patient organisations to promote the sharing of information;
- to contribute to improving the quality of life of patients suffering with rare disease in Japan and internationally by cooperating with support organisations worldwide;
- to launch a basic research project for rare diseases called the 'PRiG Project' with the National Institute of Genetics and Tokai University School of Medicine in Japan.

The PRiG Project was launched in September 2010 to improve the basic environment for research and development of new treatment methods and medicines for rare diseases by using the latest science technologies, including establishing a Cell Bank of 'iPS cells' and a Genome Information Bank.

Induced pluripotent stem cells (iPS cells) are cells that have the ability to develop into a variety of human cells and to

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replicate and grow almost infinitely. The stem cell bank will be established from rare disease patients' blood and will be provided to researchers and research institutions around the world that are willing to study them for finding cures and developing therapeutic products in the field of rare diseases, in particular those rare diseases that are not covered by the Research Program for Overcoming Intractable Disease led by the Japanese government.

The Genome Information Bank will store information on disease-causing genes identified by analysing the whole genome of rare disease patients, and the banked genetic information can then be used in both research and clinical fields, such as in making disease-model animals needed for research or in confirming diagnosis for patients who have been undiagnosed.

5.5 External links and sources of further information

5.5.1 USA

FDA – Common EMEA/FDA Application for Orphan Medical Product Designation: *www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseases Conditions/HowtoapplyforOrphanProductDesignation/ UCM135127.pdf*

NCATS: *www.nih.gov/about/director/ncats/index.htm*

NCATS podcast: *http://ocplmedia.od.nih.gov/nihradio/ NCATS%20audio.mp3*

National Organization for Rare Disorders (NORD): *www. rarediseases.org*

NIH ORDR: *http://rarediseases.info.nih.gov/*

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TRND: *www.ncats.nih.gov/research/rare-diseases/trnd/trnd.html*

5.5.2 EU

Belgium National Plan for Rare Diseases: (French) *www.kbs-frb.be/publication.aspx?id=271066&LangType=2060* (Dutch) *www.kbs-frb.be/publication.aspx?id=271066&LangType=2067*

EU Community Research and Development Information Service (CORDIS): *http://cordis.europa.eu/fp7/health/*

EU Executive Agency for Health and Consumers: RARE DISEASES CONFERENCE 2011 – Video: *http://ec.europa.eu/eahc/health/Rare_Diseases_conference_2011_video.html*

EU High Level Pharmaceutical Forum Conclusions on 'Improving Access to Orphan Medicines for All Affected EU Citizens': *http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf*

EUnetHTA: *www.eunethta.net*

European Commission – Corporate Responsibility in the Field of Pharmaceuticals: *http://ec.europa.eu/enterprise/sectors/healthcare/process_on_corporate_responsibility/index_en.htm*

European Commission – Directorate-General Health and Consumers: Events 'Video: Commissioner Dalli visits the European Medicines Agency in London': *http://ec.europa.eu/health/human-use/events/ev_20120206_en.htm*

European Commission call for tender to conduct study on 'The creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan

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medicines': *http://ec.europa.eu/eahc/health/tenders_H05_2010.html*

European Commission Communication on 'Rare Diseases: Europe's Challenges' *http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf*

European Council Recommendation on a European 'Action in the Field of Rare Diseases' *http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF*

European Project for Rare Diseases National Plans Development (EUROPLAN): *www.europlanproject.eu*

EURORDIS: *www.eurordis.org/content/eurordis-advocating-improve-patient-accessorphan-drugs-europe*

Swedish Presidency EU Project: *www.lakemedelsverket.se/english/overview/About-MPA/EU-Presidency–2009/Meetings/Assessing-Drug-effectiveness/*

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Designing robust clinical trials for orphan drugs

With additional contributions by Gordana Tankovic

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Abstract: Though registration requirements for orphan drugs are not fundamentally different from other medicinal products, obvious obstacles are given by the limited number of patients with a specific rare disease, and flexibility and efficiency are needed in the development process. Frequently, the natural history of the disease is unknown, there are typically no established study endpoints, and placebo use may pose ethical problems. Adaptive trials and repetitive design may be used. As the conditions are frequently life threatening and lack existing treatment, conditional marketing approval may be granted on the basis of limited data or under exceptional circumstances. Open safety and efficacy questions are subject to post-marketing commitments.

Key words: study design, endpoints, sample size, *p*-value, approval, HTA, post-marketing commitments.

Since the Orphan Drug Act of 1983 was signed into law in the USA, 2730 products in development have been designated as orphan drugs, while the FDA has granted market approval

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to 421 drugs up to 31 December 2012. (Online search tool: *www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*)

Historically, the FDA grants approval for all new drugs on the basis of 'substantial evidence' for safety and efficacy demonstrated in 'adequate and well-controlled investigations' and there are no exemptions (21 CFR §314.105), special provisions or specific guidance on orphan drugs. Adequate and well-controlled studies shall be designed to distinguish the effect of a treatment from other influences (e.g. spontaneous change, placebo effect, biased observation). The priority is to protect the consumer by ensuring that only adequately qualified drugs enter the market. A balance must be found between having sufficient evidence on the risk and benefits of new therapies and not unduly withholding life-saving medicines from the severely ill waiting for treatment. As the FDA is aware of the practical difficulties with orphan drugs in clinical research imposed by the low number of affected patients with a specific disease, the review process of orphan medicines is done on a flexible, case-by-case and scenario-driven basis within the current regulatory provisions (Table 6.1).

To help in this area the FDA, in collaboration with the NIH ORDR and the NCATS, has run a Small Clinical Trials Course, and further information is available from: *https://events-support.com/events/FDA-NIH_Science_Small_Clinical_Trials/page/167*

NORD analysed 135 US orphan drug approvals from 1983 to 2010 and found in 32 successful applications evidence of administrative flexibility by the FDA in the evaluation, in 58 approvals case-by-case flexibility and in the remaining 45 applications a conventional basis for approval with evidence of two well-controlled clinical studies (Sasinowski 2011).

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Table 6.1 **Examples of regulatory flexibility applied to drug and biological product approvals by FDA for rare disease indications**

Drug (*trade name*) [rare disease indication]	Special consideration for the rare disease circumstance in basis of approval
Inactivated Japanese encephalitis virus vaccine (*Ixiaro*) [prevention of Japanese encephalitis]	Surrogate endpoint
Human fibrinogen concentrate (*RiaSTap*) [congenital fibrinogen deficiency]	Clinical experience in Europe; surrogate endpoint
Tetrabenazine (*Xenazine*) [Huntington's disease]	Results of a single study
Agalsidase beta (*Fabrazyme*) [Fabry disease]	Results of a single study; surrogate endpoint
Imatinib mesylate (*Gleevec*) [GIST tumors]	Results of a single study; surrogate endpoint (Subsequent approval based on one multi-disease open-label phase 2 trial without a comparator arm and on published case reports for a variety of rare tumours expressing the molecular targets of imatinib)
Alglucosidase alfa (*Myozyme*) [Pompe disease]	Results of a single study; historical control group

Source: Modified from Hamburg (2011).

Though interpretation of statutory standards varies and relevant inconsistencies in review practice have been observed between FDA Divisions, taken as a whole orphan products have a 37% higher probability of FDA approval (NDA: orphan drugs 22% approval, non-orphan drugs 16%) (Tufts CSDD 2010) and a 47% lower regulatory review time on

average as reported by the Boston-based strategy consulting firm Putnam Associates in 2011 (Putnam Associates 2011).

In many instances, the overall clinical development programme is similar to approaches used for development of paediatric or cancer drugs. As with other drug development for human use, product development of orphan drugs proceeds stepwise and in four phases during clinical development: after the discovery phase (target, therapeutics), non-clinical safety testing (animal and in vitro studies) and process development for manufacturing of large-scale batches, regulatory authorities may approve entry into the human phase. The manufacturability of biologics needed in much higher amounts than for animal experimentation is frequently a key element of decision-making when selecting between development candidates for entry into the human phase in addition to an appropriate safety profile. In human pharmacology studies in a limited number of patients or healthy subjects (Phase I), safety and tolerability are tested and data on pharmacokinetic (changes in drug plasma concentrations after dosing) and pharmacodynamic parameters (changes of biological parameters with time and dose) are generated. This is followed by therapeutic exploratory studies (Phase II), which intend to define the therapeutic dose range and to further characterise the drug's safety profile in the target population.

Thereafter, large-scale trials (Phase III) will be conducted to demonstrate the drug's efficacy and safety at the selected dose with patients fulfilling certain inclusion and exclusion criteria. This may be done in a comparative parallel group trial with patients randomly assigned to the investigational drug, placebo (dummy-drug), and/or an active comparator drug with established efficacy for the investigated condition. Such randomised controlled trials (RCT) are considered the gold standard. Typically, primary endpoints of pivotal studies

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are used to support the claimed indication, and secondary endpoints may help to differentiate from competitor products or to support additional labelling information. Generally, supporting evidence from two pivotal studies is needed, but in certain exceptional circumstances (e.g. evidence from a large multicentre study, consistency across study subsets, properly designed factorial studies, multiple endpoints involving different events, statistically very persuasive findings) a single adequate and well-controlled study giving compelling evidence may be a sufficient scientific and legal basis for approval (US FDA 1998; CPMP/EWP/2330/99; Milne 2002; Peck and Wechsler 2002).

Sometimes, exploratory human studies (Phase 0) are conducted in the development of drugs for serious or life-threatening diseases at entry into the human phase, which may investigate absorption of microdoses and involve fewer resources to make Go/No Go decisions during substance selection. For common medical conditions, the cumulative patient exposure at the end of the clinical development programme includes typically several thousand patients (ICH E1A). Nevertheless, after approval (Phase IV), further safety data will be collected in observational studies in unselected patients under clinical practice conditions or from spontaneous reporting of adverse drug reactions.

Repurposing of an approved drug for an orphan disease may already provide a preliminary basis for pharmacology and safety data, which must be supplemented by results in the patient target population (and a supplemental NDA (US) may be filed).

As an aside, and to assist in drug development, the FDA's OOPD has established an RDRD of products that:

- have received orphan status designation (i.e. they've been found 'promising' for treating a rare disease) and;

- are already market-approved for the treatment of some *other* diseases up through June 2010.

(www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm)

Using this approach, Sildenafil, initially approved for erectile dysfunction, was additionally approved to improve exercise ability of patients with idiopathic pulmonary arterial hypertension (Revatio®). Similarly, Afinitor® (everolimus) was approved for the treatment of patients with subependymal giant-cell astrocytoma on evidence from one single-arm clinical trial in 28 patients in conjunction with data of Zortress®, which was originally approved as an immunosuppressant for the prophylaxis of organ rejection (Curran 2012).

For orphan drugs, the limits between development phases may not be clear-cut and sometimes approval may be granted without a typical clinical trial programme. Though it is specified that the minimum exposure requested for conventional drugs according to international regulations (ICH E1A) does not apply to orphan drugs, it is not defined what is expected. This allows flexibility for individual features of unique drug applications based on scientific judgement, but otherwise causes uncertainty for drug manufacturers on what to provide with the approval package. Early regulatory advice may reduce the development risk for the industry, but though useful, those scientific recommendations given in advance are not binding to the final reviewer. Lack of binding policy regarding specific regulatory requirements for approval of orphan drugs in the USA is a risk perceived both by the industry and advocacy groups. Though sometimes Special Protocol Assessment

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(SPA)[1] by the FDA can be achieved, the process is unpredictable and frequently lengthy.

Clinical phase orphan drug development typically starts with an orphan drug designation (ODD). Until now, more than 1000 orphan drug designations have been granted in the EU. In most cases, at an early stage, scientific advice meetings regarding protocol assistance or pre-submission meetings are held with the EMA or the FDA or other agencies. In the EU, scientific advice for assisting in protocol development of orphan drugs is free of charge for SMEs (EMA 663496/2012).

As with other drugs to treat serious diseases and which fill an unmet medical need, obtaining a Fast Track designation with the FDA is possible. This entitles the sponsor to access to a rolling review of the product dossier and eligibility for an accelerated approval. To save time to market and making life-saving medicines available for patients as soon as possible, accelerated approval may be granted on the basis of indirect biological markers that are reasonably likely to be predictive of a drug's effectiveness, that is, validated biomarkers / surrogate endpoints (e.g. tumour size), instead of clinical outcome (e.g. survival). But to complement missing evidence, the marketing authorisation holder is obliged to demonstrate actual clinical benefit by conducting confirmatory trials in the post-marketing phase. For drugs that offer major advances in treatment, additionally Priority Review by the FDA may apply, which may save approximately another 6 months compared with the standard review time.

Similar provisions apply to the accelerated evaluation of products indicated for serious, life-threatening or heavily disabling diseases in the EU (CPMP/495/96 rev 1).

Medicines might receive approval in the EU under any of three different headings: normal approval, approval under exceptional circumstances, and conditional approval. Approval under exceptional circumstances might be given

when comprehensive data cannot be provided, for instance because of the rarity of the disease or because of ethical barriers. Such an approval is granted on the basis of specific obligations of the licence holder to inform the regulator about safety and efficacy with the passage of time. The EMA might grant conditional approval for one year, renewable, when the dataset submitted is incomplete, but there is a positive risk–benefit balance evident from that available as long as the licence holder provides comprehensive clinical data after approval. Assessment of the benefits and risks of this approach will take some time to emerge (Buckley 2008).

In contrast to the USA, a dedicated EU Guideline (CHMP/EWP/83561/2005) exists on clinical trials in small populations. In addition, several other EU regulatory documents govern further details specific to the development of orphan products:

- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005);
- Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, 9 July 2007 (ENTR/6283/00 Rev 3);
- Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009);
- Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation (EMA/COMP/436/01);
- Regulation of the European Parliament and of the Council on medicinal products for paediatric use (EC 1901/2006).

Similar to conventional medicines and in contrast to the intended purpose of that convention, approval in one

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[2] region is not sufficient to qualify an orphan drug for marketing authorisation elsewhere. The EMA approved both agalsidase beta (Fabrazyme®, Genzyme Corporation, produced in Chinese hamster ovary cells) and agalsidase alfa (Replagal, Shire Human Genetic Therapies, Inc., produced in human cell lines) in the EU for treatment of patients with Fabry disease (FD), and a comparative study (Vedder et al. 2007) showed no difference between treatments after 24 months (reduction of left ventricular mass, n = 34 patients).

Mitsumoto et al. (2009) compared approvals for drugs for neurological diseases with an orphan indication (n = 19) and without an orphan indication (n = 20). All drugs for neurological diseases (100%) approved without an orphan indication included at least two randomised, double-blind, placebo-controlled trials. In comparison, 32% of drugs with an orphan indication had at least two such trials ($p < 0.001$) and 74% had at least one ($p = 0.02$). Thirty-three pivotal trials were conducted for the 19 drugs approved with an orphan indication. Of the 33 trials, 11 (33%) did not use a placebo control, 9 (27%) were not double blind, and 4 (12%) were not randomised. Drugs approved without an orphan indication had more pivotal trials per drug (3.8 v. 1.7 trials; $p < 0.001$) and a larger mean trial size (506 v. 164 trial participants; $p < 0.001$).

6.1 Review of hurdles and implications for study design

The most obvious obstacle for conducting clinical studies in rare diseases is the lack of affected patients. They may be

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scattered worldwide or clustered in a specific geographic area. Enrolling a large patient cohort for a clinical trial is inherently demanding or may not be practical. Thus some drugs for rare diseases were approved without any formal trials: betaine for homocystinuria was approved in the EU on the basis of 202 spontaneous literature reports and hydroxycarbamide for sickle cell disease on the basis of bibliographic data and registries.

Despite the constraints and many challenges, no methods exist that are relevant to small studies that are not also applicable to large studies. Taking orphan drugs approved in the US market during 2010 as an example, it is obvious that most pivotal studies did not differ principally in design and control from other drug applications, though programme size varied from 23 to 540 patients, other supporting evidence (published literature, compassionate use information, existing approvals in other ICH regions) was sometimes included, and clinical evidence may be derived from a single study (Table 6.2).

Adcetris® (brentuximab vedotin; for Hodgkin's lymphoma and systemic anaplastic large cell lymphoma) was given an FDA Fast Track designation for its potential to address an unmet medical need and was reviewed under the FDA's priority review programme. The effectiveness of Adcetris® in patients with Hodgkin's disease and anaplastic lymphoma was evaluated in a single uncontrolled clinical trial (102 patients and 58 patients, respectively) with objective response rate (tumour shrinkage as a surrogate endpoint) as primary endpoint (US FDA 2011a).

The effectiveness of Caprelsa® (vandetanib) for medullary thyroid cancer was established in a randomised, placebo-controlled study (331 patients) with the period of time without disease progression as the primary endpoint, without a second pivotal study being requested. Firazyr® (icatibant) (which can

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Table 6.2 CDER Orphan approvals in 2010

Product	Indication	Type	Exposure (program)	Pivotal	Design	Primary endpoint
Dalfampridine (Ampyra®, Acorda)	Improve walking in Multiple Sclerosis	NDA	n=540	2 trials	RND, DB, PC	Responder analysis (proportion within group) of increase in average (25-foot) walking speed change from baseline
Collagenase (Xiaflex®, Auxilium)	Dupuytren's contracture	BLA	n=374	2 trials	RND, DB, PC	Proportion of patients who achieved a reduction in contracture of the selected primary joint 30 days after the last injection
Velaglucerase (VPRIV®, Shire HGT)	Gaucher disease	NDA	n=99 (3 studies)	1 study (n=25)	RND, DB	Mean change of haemoglobin concentration from baseline between low-dose and high-dose groups at endpoint
Carglumic acid (Carbaglu®, Orphan Europe)	N-acetylglutamate synthase deficiency	NDA	n=23	1 case series	OL, Hx controlled	Time course of plasma ammonia concentration

(*continued overleaf*)

Table 6.2 (*continued*)

Product	Indication	Type	Exposure (program)	Pivotal	Design	Primary endpoint
Alglucosidase alfa (Lumizyme®, Genzyme)	Late-onset Pompe disease	BLA	Supportive evidence from post-marketing registry of *infantile*-onset form (n=15)	1 study (n=90)	RND, DB, PC	Difference between treatments groups (active, placebo) in mean forced vital capacity and mean 6-min walk test at endpoint
Glycopyrrulate (Cuvposa®, Shionogi)	Drooling in children with neurologic disorders	NDA	n=151 (2 studies)	1 study (n=38)	RND, DB, PC	Proportion of responders at Week 8 defined as at least a 3-point reduction in mean daily 9-point modified Teacher's Drooling Scale scores from baseline
Pegloticase (Krystexxa®, Savient Pharma)	Chronic gout not responsive to conventional therapy	BLA	n=212	2 trials	RND, DB, PC	Proportion of patients with plasma uric acid less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6

BLA Biologics Licence Application, DB double-blind, Hx historical, n number of patients, NDA New Drug Application, OL open label, PC placebo-controlled, RND randomised.
Source: Modified from: Pariser (2010).

be self-administered) was approved as the third drug to treat acute attacks of hereditary angioedema with evidence from three small controlled clinical trials (two placebo-controlled trials, one active-controlled trial) with open-label extension (225 patients). Corifact® (human Factor XIII concentrate) was approved based on the results of a pharmacokinetic study in 14 patients, with the commitment that clinical benefit will be verified in a post-marketing study to measure the prevention of spontaneous bleeding episodes. Anascorp® (Centruroides equine antibody F(ab')2) was approved to treat clinical signs of scorpion envenomation based on results of a randomised, double-blind, placebo-controlled trial of 15 children with neurological signs of scorpion stings.

Despite successful applications, many obstacles remain in conducting orphan drug trials (Box 6.1). Less conventional

Box 6.1

Challenges in the Design of Orphan Drug Studies

- Complex logistical issues (few and disseminated patients)
- Ethical issues (use of placebo, research in vulnerable populations including mentally impaired and children)
- Disease heterogeneity in manifestation and fluctuation of severity
- Limited knowledge of disease natural history
- Lack of accepted clinical efficacy outcome measures
- No established minimum clinically important difference
- Validation of biomarkers
- Absence of animal models for diseases

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and/or less commonly seen methodological approaches are therefore sometimes needed and may be acceptable if they help to improve the interpretability of the study results (CHMP/EWP/83561/2005). There is no single best strategy for successful clinical development of orphan drugs and the most appropriate approach may be dependent on many factors. In many instances, there is no path to follow from a previously approved drug for a rare disease indication.

Frequently the number of patients with a specific rare disease is not only small, but the study population must be collected worldwide, which adds to the complexity and costs of rare disease trials. In the development of Myozyme®, patients were retrieved from all over the globe and only one patient of 39 study participants at eight sites in five countries did not have to relocate. This included bringing patients and their families to other continents, foreign cultures or adversarial political systems: from Japan to the UK, from Peru to the USA, from the Gaza Strip to Israel. Parents had to quit jobs; families needed housing for several months, assistance with travel, funding, interpreters, immigration support; and children had to attend new schools. Assistance was provided by partnering of the manufacturer with NORD. Affected patients were identified through announcements at medical conferences, sending more than 25 000 letters to individual physicians, and finally by word-of-mouth (Genzyme 2005).

Some human pharmacology studies may be conducted in healthy adults instead of rare disease patients. This may not be possible with treatments involving high risk or toxicity and drugs that target a certain metabolic pathology that is not present in healthy subjects, and therefore the validity of extrapolation may be uncertain (e.g. N-acetylglutamate synthase deficiency). Additionally, many rare diseases present heterogeneously with different systems, disease severity, and

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clinical course throughout the patient population as in the case of rare lung diseases (Luisetti et al. 2012).

In many cases, patient registries can address various issues related to the rareness of affected patients: the collected data may provide information on the natural history of the disease (e.g. survival), help in the selection of suitable treatment periods when the disease progresses slowly, and supply historical controls for external comparison of study data. They may be linked to collections of biological specimens, which may reduce the time for finding biomarkers. Data use and protection of donor privacy in the EU is subject to the Data Protection Directive, EC Directive 95/46/EC, but the collection, storage and sharing of biological samples and application of property rights in the EU and outside[3] is regulated nationally and not yet harmonised despite the international collaborations between biobanks[4] (Chalmers 2011; Haga and Beskow 2008; Schulte in den Bäumen et al. 2010; Zika et al. 2008).

Having found the patients, there is frequently the ethical problem of how to deal with non-eligible patients who suffer from the same fatal condition and are awaiting a cure. Genzyme identified 77 patients with Pompe disease, but only 39 were part of the regulatory filing. As knowledge spreads in the patient community, some additional patients may arrive unannounced at the test site. A desperate family in Italy chained themselves to a hospital fence and initiated a hunger strike to draw attention to their affected baby. Compassionate use of the new treatment was offered through a special expanded access programme, but production capacity was stretched to the limit.

Moreover, it must be kept in mind when conducting clinical trials with rare disease patients that they belong to an especially vulnerable population of research subjects. Chronic disease patients mostly do not 'choose' to enrol in a

trial, but are chosen by their disease and a full informed consent disclosing all available treatment alternatives other than the experimental medicine is indispensable prior to all clinical research. Shortcuts like Zelen randomisation for control patients on standard therapy are ethically not acceptable if there are choices available and the decisions rightfully belong to the patients and their caregivers (Zelen 1979).

In contrast to conventional drug development programmes, which include the paediatric population late in development when sufficient human safety experience is available from adult trials, infants may be the first subjects exposed to orphan drugs, such as in the case of Myozyme®. They need lower drug quantities for treatment which accommodates limited pilot plant capacity, are frequently in an early disease stage without complications, exhibit larger effect size to treatment, and may be the patient population with the highest benefit from therapy.

The selected sample of study population must be a representative sample of the entire population affected by the disease under investigation in order to ensure external validity of the study (i.e. the study results may be extrapolated to the entire group of patients). External validity may be checked by analysis of data in screening logs by demonstration that the enrolled and excluded patients are not different.

As described above, the degree of evidence (see also Box 6.2) provided as the basis of approval may vary between orphan drugs applications, and both classic development programmes and observational results of case series may lead to approval. In most instances, evidence of drug efficacy is generated by RCTs. Results of several small controlled studies may be combined in a meta-analysis. Though it is not a simple exercise to weigh evidence from small high quality evidence trials against larger data from uncontrolled case

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Box 6.2

Hierarchy of Study Designs (CHMP/EWP/83561/2005)

- Meta-analyses of 'good quality' RCTs
- Individual RCTs
- Meta-analyses of observational studies
- Individual observational studies
- Published case reports
- Anecdotal case reports
- Opinion of experts

series, observational studies and individual case reports may be the basis of approval in exceptional circumstances.

In very rare diseases, the combined evaluation of single case studies may be the only way to provide evidence. In such situations, treatment conditions and data collection should be standardised, and data should be of high quality and adhere to Good Clinical Practice standards. Such studies should be prospectively planned and described in study protocols (CHMP/EWP/83561/2005).

Internal validity is achieved by a control group. The type of control determines the level of evidence that may be gained from a clinical study. Controlled studies with low statistical power in case of an important treatment effect may be preferable to no controlled studies. Conducting a randomised controlled trial should be attempted but is not always feasible with orphan drug development.

The use of a placebo in clinical studies is subject to ongoing debate in light of the current version of the Helsinki Declaration (Garattini et al. 2002; Garattini et al. 2003; Lewis et al. 2002). Nevertheless, the use of a placebo is considered acceptable by most researchers if the patient will

not be harmed by deferral of effective treatment (Temple and Ellenberg 2000) or when no therapy is available or lack of benefit to patients is negligible (Emanuel and Miller 2001). Using an active control instead of a placebo control is normally not acceptable as an alternative to demonstrate efficacy of a drug for US regulatory purposes as similarity of the test drug and the active control can mean either that both drugs were effective or that neither was effective (21CFR314.126). In particular, the use of placebo control in life-threatening conditions typically causes ethical concerns. It may be argued that the effectiveness of the new intervention is possible but not established, and a loss of benefit is uncertain. Randomisation in a ratio other than 1:1 may be used to decrease the number of subjects not getting potential benefit. Alternative designs include randomised adding to treatment after placebo-run-in or randomised withdrawal from treatment. Crossing over of patients to active therapy in an open-label extension phase may be considered. Generally, it may not be justifiable to conduct placebo-controlled studies in a later stage when results of first uncontrolled, open-label studies have been obtained.

Several modifications of classic study designs are described in current guidelines, which decrease the potential disadvantages of placebo use (ICH E10):

- It is possible to design an 'early escape' study that removes patients from ineffective therapy if their clinical status worsens.
- An add-on design may be used with patients maintained on standard of care and the subsequent addition of either placebo or the active treatment. This approach may not be used if the study drug and the standard medication have synergistic toxicities and it is not informative if both interventions share the same mode of action.

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- Similarly, when placebo use is not possible, a dose-response design may be used with patients randomly assigned to different dose levels of the investigational treatment. A positive study should demonstrate increasing efficacy with increasing dose. If the dose–response relationship is not well characterised, it may be difficult to select the appropriate dose levels. Assessment of the treatment effect size may not be possible using this design.
- Factorial designs may be used to explore combinations of several dose levels of the investigational drug with several dose levels of another agent proposed for use in combination with it.
- In a placebo-phase design (add-on) all patients start active treatment at different time points after a variable placebo phase. The individual duration of the placebo phase is randomly assigned. A positive study will demonstrate similar efficacy in all treatment groups but in a temporal manner consistent with the time at active treatment. This design may be used if treatments are highly potent. Knowledge of the time to expected treatment effect is necessary for adequate timing of interventional groups and the baseline intensity of the disease should not fluctuate until onset of therapy.
- Similarly, in a random-withdrawal design, active treatment may be stopped after different treatment duration, and disease deterioration without treatment may be demonstrated. This study design does not work with irreversible treatment effects and diseases with fluctuating baseline severity.

Internal control of a study may also be achieved in a crossover trial with a patient assigned to both treatments in random order, thus serving as its own control. The advantage is lower patient numbers compared with a parallel group trial and a

higher patient acceptance as maximum exposure to inactive placebo is only 50%. The design is suitable for short trials with rapid response as long-term fluctuations in the course of the disease would not occur within the study period. However, the design is limited to diseases that have comparable severity at the beginning of both periods and to drugs with a half-life that permits wash-out in a couple of days to avoid carry-over. Similarly, patients may be randomly assigned or withdrawn from treatment. Also, in this case a drug with a long half-life may not be assessed.

If an established treatment is available, a trial with this drug as an active comparator, either blinded or unblinded, may be conducted to internally control the study. If only active controlled studies are conducted, assay sensitivity of the study cannot be assured, but data on the natural course of a disease may help to estimate study sensitivity. If treatments are essentially similar, assay sensitivity is not an issue. A study (funded by Dutch payers) compared agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) in a randomised, open-label study (n = 34) in order to show the biosimilarity of the two orphan medicines (Vedder et al. 2007).

Both ethical concerns and the limited number of available patients may lead to the decision to run a study as an open-label uncontrolled trial. Non-randomised, open-label studies were used to support approval of cysteamine for nephropathic cystinosis and sodium phenylbutyrate for urea cycle disorders. Carglumic acid (Carbaglu®) was approved on the basis of a trial of 12 patients, with retrospective data collected on an additional 20 patients. More recently, a single-arm study (18 paediatric patients) with an external historical control (61 children born between 1960 and 2003) supported the original application of Myozyme® for type I Pompe disease (NDA 125141/0, FDA CBER, Medical Review).

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Single open-label studies may nevertheless be controlled. If internal control is not possible, the effect of study treatment may be compared with external controls. An external control of the study intervention with historical data may be acceptable if the disease is well characterised and the course of the disease is invariable. Since no placebo control is used in historical controlled trials, patients are easier to recruit; however, interpreting the results of such studies may sometimes be extraordinarily difficult.

In order to conduct a trial using a historical control group (untreated patients or available standard therapy), the disease must be well differentiated, with steady and rapid progress, and be free of additional interventions during the study period (Haffner 1998). Changes in the standard treatment may affect interpretation of historical control data or render them useless, for example availability of antibiotic use for cystic fibrosis. Ceredase® for Gaucher disease and Adagen® for severe combined immunodeficiency were approved based on data comparing with historical control groups. Conducting a trial using historical controls may actually take longer, because endpoints must be controlled against what is historically known about the effectiveness of the product.

Sometimes, patient registries may be used as a source for historical controls. Frequently, there are no published data of sufficient quality available on a specific disease and patients have to be followed in a natural history study to obtain this information. Examples include the determination of life expectancy in Gaucher disease (Weinreb et al. 2008), the assessment of the incidence of stroke in patients with Fabry disease (Sims et al. 2009), and the characterisation of the baseline clinical characteristics of patients with mucopolysaccharidosis type I (Pastores et al. 2007). For this purpose, untreated patients and patients before receiving

therapy were included in a registry, the course of disease was followed, and the data were analysed.

In addition to having data for external control of the study design, issues related to the natural history of a disease are:

- the speed of disease progression may determine the study duration;
- disease heterogeneity may affect selection of study endpoints;
- imaging findings, biochemical parameters or pathologic markers may not correlate with clinical impairment such as in neurodegenerative disease;
- reversibility of the condition or delaying disease progression may be achieved;
- decisions must be taken as to whether the disease may be treated or prevention of symptoms is feasible;
- in multinational trials, problems may arise as the standard of care is frequently not defined.

Apart from design questions, the investigational drug, the target disease, the overall development strategy and the individual trial design are affected by the market environment and the activity of competitor companies. As with the development of other medicines, there is considerable entrepreneurial and commercial risk involved in clinical development given an average rate of 90% of drugs entering the human phase not achieving marketing approval. Moreover, long-term financial commitment of a substantial amount of capital for approximately 10 to 14 years of drug development is needed and orphan drug development is not necessarily faster. For small companies, raising venture capital may be the first hurdle, as public and private funding tend to donate grants mostly for basic research. For

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biologicals, scale-up of production, purity from by-products, and assurance of constant between-batch quality may be especially demanding prior to entry into the human phase. Immunotoxicity or immunogenicity may pose further pre-clinical and clinical challenges, as both animals and humans who completely lack expression of a specific protein may mount an immune response under repeated protein replacement therapy.

Existence or absence of a previously approved product has both potential positive and negative impacts on the clinical development strategy. If approved therapy exists, the knowledge of the disease is broader, study endpoints acceptable to regulators are established, and experienced study sites are known, while the number of patients willing to test a new medicine with unproven effectiveness will probably be lower and superiority over the existing treatment must be established. Diagnostic testing and establishing a diagnosis, medical and community awareness of the disease, epidemiology data and disease classification improve, after a treatment is available. Thus, the advantages of pre-existing knowledge frequently outweigh the development risks and multiple orphan drug approval has been achieved (e.g. Sprycel® and Evoltra® for ALL, Nexavar® and Sutent® for renal cell carcinoma, Sutent® and Glivec® for GIST tumours). If no treatment exists, more patients may be willing to enter a study, investigators may probably be more enthusiastic, but established outcome measures may not exist, knowledge on natural disease history can be scarce, placebo use and availability of the treatment after the study will pose ethical problems, and the upcoming availability of a potential treatment must be efficiently communicated to small patient communities living disseminated over large geographic areas. Thorough observation of patients with a rare disease under conditions of a clinical trial may reveal previously unknown

disease symptoms, which may be confounded with adverse drug effects in uncontrolled studies.

6.2 Finding relevant study endpoints

Heemstra et al. (2011) analysed the characteristics of 15 orphan drug applications that failed to achieve marketing approval in the USA between 1998 and 2007 compared with 41 successful applications. Of utmost importance was the adequate selection of the primary endpoint, and approval could not be obtained if, in a pivotal trial, efficacy on the primary endpoint (clinical or surrogate) could not be demonstrated. Additionally, the sponsor of unsuccessful applications more frequently had not yet identified the most appropriate patient population for the drug. Companies with previous orphan drug experience had higher chances for success. Obtaining FDA advice in pre-NDA meetings and adhering to the regulatory advice from the FDA in designing and conducting the pivotal clinical trials are both associated with approval.

A carefully selected study question is the starting point for developing a feasible design. The basis for it is some basic information regarding which symptoms will be targeted by the new treatment, how they appear (progressive, periodic, sporadic), what treatment duration is necessary to see clinical change in a certain disease, and how treatment effects may be quantified. At the end of a clinical study, we may compare treatment effects at a single point in time or assess changes over time observed with different therapies.

Thus a study endpoint consists of an outcome parameter analysed in a certain way, such as the myocardial infarctions after 6 months expressed as percentage of patients in the treatment group. Carefully selected endpoints should be

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sensitive to detect treatment effects and interpretable in a clinical context. In rare disease studies, it may sometimes not be possible to pre-specify the primary clinical endpoint, and collecting data on various sensible endpoints should be attempted (CHMP/EWP/83561/2005).

Clinically meaningful endpoints provide a direct measure of how a patient feels, functions or survives and are expected to predict the long-term outcome of therapy. The extremes are complete cure or death. Other examples are the overall survival in cancer, ventilator-free period in cystic fibrosis, or the number of patients with thrombosis in Marchiafava syndrome. In studies whose endpoint is time to progression or time to remission, adequate length of follow-up of the patients is important; this can be done in 'open-label extensions' or randomised studies (CHMP/EWP/83561/2005). Clinical endpoints provide a high degree of evidence for a drug's therapeutic effect, but in lengthy studies and considering drop-out over time, a high number of patients are needed for studies with clinical endpoints.

Surrogate endpoints are reasonably likely to predict the clinical outcome change more rapidly than clinical endpoints and may be used instead in order to shorten the study duration. They provide preliminary evidence of a drug's efficacy from studies of shorter duration and may curtail the time until a marketed drug is available for patients awaiting a cure. Surrogate markers are believed by current knowledge to share a causal mechanism with the clinical outcome. Pre-defined changes in a surrogate marker that are expected to predict clinical benefit may define a surrogate endpoint. The expectations of the regulatory agencies are not well defined as to how much evidence is needed to show that a surrogate endpoint is reasonably likely to predict benefit. Fleming (2005) proposed some criteria for acceptable surrogate markers: accurate presentation of the clinical

outcome, full capture of the net effect, clinical evidence that the intervention is not adverse, strong and durable effect, and specificity to a drug's mode of action. Validation of surrogate markers can be complicated and expensive. Using surrogate endpoints (e.g. forced expiratory volume in one second for cystic fibrosis) is considered acceptable in life-threatening conditions, as a higher risk associated with treatment is tolerated compared with less serious conditions. The missing evidence of effectiveness is usually supplemented by post-marketing study data.

Miyamoto and Kakkis (2011) compared the presumptive cost of development for drugs using clinical or surrogate endpoints in 15 inherited disorders of metabolism. Thus, for example, urinary oxalate might be measured (with 20 patients in a 6-month study) instead of renal failure (with 183 patients in a 2-year study) in primary hyperoxaluria. The estimated sample size, trial duration, and time to market may decrease markedly by use of surrogate endpoints, leading to expected savings in development costs of between 38% and 71%.

Biochemical markers (plasma homocystine for homocystinuria with Cystadane®), imaging parameters (liver size for Gaucher disease with Ceredase®), and pathologic endpoints (score of renal pathology for Fabry disease with Fabrazyme®) have been used as surrogate endpoints for the approval of orphan drugs. However, starting in the research phase, our understanding of a specific rare disease is frequently incomplete, which limits entry into the clinical phase, for example by absence of biomarkers that describe the course of the disease and allow measuring of response to potential treatments. The molecular pathogenesis is well known for only a small number of the approximately 5000 to 8000 rare diseases and the specific gene alteration in an even smaller subgroup. In addition, sometimes there are no established animal models and generation of knock-out and

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transgenic animals requires adequate facilities and expert knowledge in the field.

Martell et al. 2011 have described the research on how they identified potential biomarkers for mucopolysaccharidosis type IVA. A total of 88 candidate biomarkers (quantitative multiplexed assays covering different biological pathways) were compared in plasma samples from healthy controls (n = 50) and untreated patients (n = 78), then a subset of patients was treated with ERT for 36 weeks and the biomarker panel analysed. Correlation analysis was conducted (age, endurance, or urinary keratin sulphate). Nineteen candidate biomarkers were significantly different between patients and unaffected individuals. Of these, five also changed significantly in response to therapy. These biomarkers need further investigation in order to elucidate their pathophysiological role.

Some proposed biomarkers such as the concentration of very long chain fatty acids in plasma in adrenoleukodystrophy, which does not present the cerebral impairment, failed to be predictive for the clinical course.

Biomarkers are traditionally used to evaluate short-range responsiveness to characterise the dose range in pharmacodynamic studies or proof-of-concept clinical studies. Limitations are that they reflect biological response but not necessarily (overall) clinical efficacy. Mechanistic biomarkers provide a linkage between the drug's mode of action and the molecular basis of disease. The link to the disease must be established in a validation step that shows that they are specific, reproducible, have prognostic value, etc. Validation of biomarkers is, even for common conditions, not a trivial step and may not be achieved with small patient groups, such as in rare diseases. If available, a validated biomarker can serve as a surrogate endpoint in a clinical trial to replace clinical outcome endpoints.

In addition to their roles as study endpoints, biomarkers may help to optimise planned clinical trials or to make them unnecessary. Thus biomarkers are used in dose-response studies and pharmacokinetic/pharmacodynamic studies to provide supportive or confirmatory evidence of efficacy. The results of these studies may be combined with pharmacometric approaches (modelling and simulation and/or clinical trial simulation) to propose optimal designs (power, degree of information generated) for late-stage clinical development trials or to directly support the application (Bhattaram et al. 2007, Li et al. 2010, Madabushi et al. 2011, Zhao et al. 2011). An example is the CRESim ('Child-Rare-Euro-Simulation') project that uses clinical trial modelling with Monte Carlo simulation in order to find optimal designs in different rare diseases.

We may take Gaucher disease as an example to illustrate the selection of biomarkers and study endpoints. A deficient expression of glucocerebrosidase is the underlying genetic cause. An increase in glucocerebroside is observed in the biochemical tests. In addition, changes in monocytes and macrophages in the spleen, liver, bone and lung are observed on a cellular level. Reduction of splenomegaly and hepatomegaly and improvement of low haemoglobin and platelet count were used as outcome parameters in the original trial leading to approval of Ceredase®.

In contrast, mucopolysaccharidosis I (Hurler-Scheie) is an example of a rare disease with a marked patient-to-patient heterogeneity where some of them display severe sleep apnoea, others not, and others require a tracheostomy. The liver may or may not be grossly enlarged. Joint disease may be mild or severe. Finding a single study endpoint presenting in patients in a small cohort may be challenging under these circumstances. Patient selection may be restricted to certain symptoms (i.e. without walking impairment), some general

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feature may be selected (i.e. the degree of breathing impairment), or a composite endpoint covering the whole spectrum of relevant disease manifestations may be constructed.

If the change from baseline to the end of treatment is assessed, then an accurate measurement and exact definition of the baseline is critical. Baseline variability is a frequent issue. The mean of repeat measurements or the most recent data point prior to treatment may be used. Thus, changes in lung vital capacity (FVC) and walking distance (6-min walking test) after 26 weeks were selected as co-primary endpoints and changes in liver volume and shoulder flexion as secondary endpoints for the Aldurazyme® phase III study (n = 45). A statistically significant treatment difference was found with regard to both primary endpoints.

Demonstration of a statistical difference over placebo is necessary, but this alone is not sufficient to support efficacy of a drug. The size of the treatment effect may statistically differ between groups but can be small. For approval of medicines, the observed treatment difference should be of clinical relevance. The minimum clinically important difference (MCID), which is the smallest difference in the domain of interest that patients perceive as beneficial, is used to demonstrate the clinical relevance of observed effects (Copay et al. 2007). Knowing the MCID puts efficacy data in a context for interpretation. A potential therapy producing a higher effect than MCID would make a change in a single patient's management. As MCID is determined as mean value within a group of patients with variability in clinical outcome, there will be patients who have higher and lower values; thus a higher patient number would need to be treated to demonstrate that a patient has a benefit. The MCID from a related disease producing similar symptoms may be used, but optimally the MCID should be known for

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the specific disease. The MCID may be determined by observing patients' disease symptoms (e.g. dyspnoea) or capacities (e.g. walking) by between-patient ratings, within-patient ratings, or global ratings of change (e.g. no change, little change, much better).

In the example of mucopolysaccharidosis I, the relative change in FVC (11.3%) was slightly higher than the MCID (11%) in this study while the mean difference in 6-MWT (38 m) was actually lower than the MCID (54 m). Responder analysis compares directly intra-patient change in contrast to MCID, which compares group means. Responder analysis showed that fewer than half of the patients (42%) showed an effect using these two endpoints. Heterogeneous multisystem diseases may show different therapeutic responses in individual patients that are not optimally captured by a single endpoint, and treatment effect may become diluted by virtual non-responders (with regard to the specific target organ) when calculating group means on endpoints not representing their disease pattern.

Single clinical endpoints may not reflect patient outcome completely. By combining change across multiple endpoints, composite endpoints may be constructed that permit a comprehensive view of patient response and give a more sensitive measure for treatment effects. The prerequisite for a valid composite outcome is that all elements of the outcome are independent of each other. Clinically relevant domains must be selected, thresholds of significant cut-off for change specified, and the degree of change quantified (e.g. +1 improve, 0 unchanged, –1 decline) to define response. The proportion of patients with net improvement may be used as endpoint and the net change calculated by the improvements minus declines per patient. The selection of domains, weighting, threshold setting, scoring system, responder definition, and the planned statistical analysis need validation

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by clinical experts and confirmation from regulatory agencies. This approach addresses the multiplicity problem without requiring adjustment to the statistical type I error (ICH E9). Using a composite endpoint approach, in the above-mentioned example FVC, 6-MWT, apnoea-hypopnoea index, shoulder flexion, and visual acuity were combined, and a much higher proportion of treatment responders (59%) could be identified.

Outcome parameters vary during the course of clinical drug development to finally show clinically meaningful outcome and patient benefit. During development of eculizumab (Soliris®), a monoclonal antibody against the complement protein C5 for the paroxysmal nocturnal haemoglobinuria (Marchiafava-Micheli syndrome), it was demonstrated in the proof-of-concept study that lactate dehydrogenase as a measure of intravascular haemolysis (11 patients, 12-week study) is reduced under therapy. In the following trials, clinical benefit was documented on short-term endpoints (e.g. transfusion avoidance, haemoglobin stabilisation), and thereafter long-term study data of additional patient benefits (e.g. reduction of risk of thrombosis, progress of renal impairment) were generated. Improvement in fatigue and quality of life (QOL) was seen in all patient subgroups regardless of level of haemolysis at baseline.

Patient Reported Outcomes (PROs) are reports of the status of a patient's health condition that come directly from the patient, without interpretation of the patient's response by a clinician or anyone else (US FDA 2009). But only a few disease-specific outcome parameters are available for orphan diseases. These methods have limited precision and accuracy and are not suitable as primary endpoints in smaller studies. In chronic diseases, patients' psychological defence mechanisms may additionally decrease sensitivity (patients 'always doing great').

Health related quality of life (HRQOL) is important when patients remain severely disabled despite effective treatment. This constitutes a specific form of a patient-reported outcome measure (CHMP/EWP/139391/2004). However, validation of HRQOL scales may be difficult in the target disease because of the rareness of affected patients. An improvement in quality of life (e.g. with regard to activities of daily life, social functioning) in the absence of any other clinical benefit is unlikely to lead to drug approval, but is considered valuable supportive evidence (CHMP/EWP/83561/2005).

6.3 Sample size and demonstration of superiority for market approval and HTA evaluation

Whenever feasible, studies should be conducted with sufficient participants to ensure adequate power for answering the research question. However, if this is not possible in the clinical context and the well-defined research question is of significance, small clinical trials may still provide a valuable piece of evidence regarding the efficacy of interventions.

Small trials are those that, irrespective of the absolute number, are insufficient to definitely answer a scientific problem (Evans and Ildstad 2001). They may be conducted in a small population such as in the case of rare diseases, emergency situations or by budget constraints. Small clinical trials are more prone to variability and may only be adequately powered to detect large intervention effects. Large treatment differences may be observed with fewer subjects. If the size of the difference one wants to detect doubles, the sample size is reduced to approximately one

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fourth. Both the treatment difference that may be reasonably expected for the new therapy and the smallest clinical important difference in the specific disease affect the estimate (Stenning and Parmar 2002). Small changes in design parameters may yield large changes in power. Hence, adequate planning is crucial especially if non-standard designs are used. But whenever possible, standard statistical methods and trial design should be applied as well in the development of orphan drugs in order to avoid problems with regulatory acceptance in the application for marketing approval.

In a randomised placebo-controlled study design, patients are randomly assigned to two or more parallel treatment groups, which include a control arm. The aim is to demonstrate superiority of the investigational treatment to placebo. Use of placebo in the control group may cause ethical issues in fatal diseases. As RCTs are almost always double-blind, bias is minimised and they are considered the gold standard of clinical trials. Randomised controlled studies are typically used to evaluate differences in group means of treatment effect of different interventions over a period of time. The sample size is pre-specified, fixed and relatively large.

According to the ultimate goal of development, the intended claim, and mode of action of a drug, the choice of study design and respective sample size may be different, for example if in a chronic progressive disease, symptomatic improvement, disease modifying effect or prevention before onset of symptoms shall be demonstrated. Randomised withdrawal design and randomised start design (see section 6.1) may be used to demonstrate a disease modifying effect.

As mentioned before, the selection of adequate outcome parameters is critical to detect the effect of treatments.

Outcome may be categorical (e.g. response or non-response with the proportion of responders per treatment analysed), continuous (e.g. liver size and the difference of means between groups analysed) or longitudinal (e.g. time to ventilator treatment and the difference in rate analysed). To measure continuous outcomes, a higher sample size is needed than for longitudinal outcome parameters, but less than categorical parameters.

Continuous outcome data may be analysed by parametric and non-parametric tests. When the response distribution is not normal, non-parametric tests (which make no assumptions about the distribution from which the sample was drawn e.g. Wilcoxon rank sum test, Kruskal-Wallis test, Friedman test) comparing medians (instead of means) may be used, but regulatory acceptance may not be given. For very small sample sizes, non-parametric tests cannot achieve statistical significance, no matter the response.

Parametric tests (T-test, ANOVA, Pearson coefficient of correlation) are slightly more powerful when data are normally distributed. Parametric tests make assumptions about data, and complex models may be developed. If only limited data are available, the most efficient analytical method must be applied to extract as much information as possible. Though non-verifiable assumptions must be made when statistical models are used, additional information will be gained compared with descriptive methods. Different assumptions, models and sensitivity analyses should be presented in order to see whether robust results may be obtained.

Repeated measurements for longitudinal data over time may improve the efficiency of an analysis. Such data are not independent between observations and mixed-effects models, hierarchical linear models, generalised estimated equations and related methods must be used for statistical analysis.

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Bayesian approaches (hierarchical models, decision analysis, predictive analysis) allow incorporating prior knowledge (belief, assumptions, data) formally into the trial design (Berry 2006; Goodman and Sladky 2005; Spiegelhalter et al. 1993; Spiegelhalter et al. 1994). Strength is 'borrowed' for the current trial from the treatment and/or the control group of a previous trial. This may be advantageous with small datasets, but introducing prior assumptions is a concern (Brown et al. 1987; US FDA 2010a).

As mentioned before, cumulative evidence of pooled trials in a meta-analysis may also help to gain maximum information from a limited set of data.

With orphan drugs, most frequently the necessary sample size to conduct a clinical study with parallel groups of patients may not be accrued with the small number of available patients suffering from a specific disease and alternative trial designs (Box 6.3) may be used. They will be described briefly in the following, but a comprehensive discussion of these designs and the related statistical methods is out of scope of this introductory text. These designs and other approaches applicable to small clinical trials

Box 6.3

Alternative Designs for Clinical Trials

- Parallel group design
- Crossover design
- Response-adaptive methods
- Group-sequential designs
- Adaptive trial designs
- n-of-1 design

have recently been reviewed in depth by Gerß and Köpcke (2010).

As discussed in the context of controlling a study, in a crossover design, each subject serves as their own control. Depending on the correlation coefficient among the repeated measurements of the primary endpoint, half or considerably fewer subjects will be needed compared with a parallel group study (Wang and Bakhai 2005). In addition, a crossover design provides the least-biased estimates for the treatment difference if the subject's response is consistently reproducible. Treatments are compared in sequential order within periods separated by wash-out periods prior to the next intervention. All treatments are given to each patient, but the order of treatments may differ between patients and is randomly assigned. Due to decreased variability, the design requires fewer patients than parallel group trials, but the conduct of the study will take longer when treatments are given in a sequential order. The analysis may be complicated by missing data when patients drop out before completing all treatment periods. The design may not be used if the intervention is not reversible or if the disease baseline is not stable, and therefore typically effects are compared that can be observed after short courses of treatment.

Several alternative designs have been proposed, which may be used in order to reduce the sample size or increase statistical power. A large reference list for the statistical literature related to these designs is contained in Evans and Ildstad (2001).

Response-adaptive methods (Biswas and Bhattacharya 2012; Rosenberger and Lachin 1993) shift the allocation to treatment (from 1:1) to the more effective intervention ('play-the-winner') before the next patients will be included. Thus outcome data must be available quickly, which is not possible very often with clinical outcomes, but is sometimes

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available with the use of biomarkers. Extremely unbalanced allocations to treatment may occur with a simple play-the-winner design (i.e. 50/50 randomisation was guaranteed only for the first patient) in small trials. This was seen in the case of extracorporeal membrane oxygenation trials in neonates with persistent pulmonary hypertension (10 + 1), which gave scientifically indecisive results about the original research question but was in the best interests of the patients under the physicians' care and saved lives (Paneth and Wallenstein 1985).

Sequential study designs include group-sequential methods and adaptive designs. In sequential trials, participants are sequentially enrolled into the study and assigned to treatment with changing probabilities during the course of the study (Carlin et al. 1998; Karrison et al. 2003; Kim and Demets 1992). A group sequential design allows for premature termination of a trial due to efficacy or futility. Strategies for sequential dose-response designs include up-and-down methods, stochastic approximation methods, maximum-likelihood methods and Bayesian methods. Statistical approaches have been proposed that avoid inflation of cumulative type I error with the repeated significance testing (e.g. Pocock, Continual Reassessment Method, Tsiatis, Kairalla). Adaptive trials (US FDA 2010b; CHMP/EWP/2459/02) proceed in stages and allow pre-specified modification of the design based on results of an interim data analysis (Chow and Chang 2008; Chow and Corey 2011; Kuehn 2006; Rosenberger 1996). Over time more patients will be assigned to the more successful treatment. Outcome data must be available quickly for making the adaption. Depending on the size of effect, these methods allow a reduction in the necessary sample size (CHMP/EWP/2459/02). Two-stage seamless adaptive designs have been proposed to extend Phase II to Phase III studies. However, a design

modification is a perceived contradiction to the confirmatory nature of late phase pivotal studies and generally needs justification. Potential benefits must be weighed against the challenges of these designs. Statistical, operational and regulatory issues may apply as described in detail by Chow and Corey (2011).

N-of-1 trials compare different interventions given in random order within a single patient (Fleming 1982; Johannessen 1991; Zucker et al. 1997). In order to make more general conclusions, a series of n-of-1 trials may be conducted to define trends (Zucker et al. 2010). Many limitations of crossover studies apply to this design as well.

Usually, the primary statistical testing of clinical trial results is done by demonstrating that a difference between the two or more experimental interventions is not caused by chance alone. Interpretation is based on the expected frequency of events.

A significance test is used and conclusions have a risk for the consumer and the manufacturer to be wrong. The risk of false positive conclusions is controlled by setting an upper bound and, by convention, 5% is accepted for this purpose. This threshold presents the consumer risk (type I error, alpha) for having an ineffective drug, that is, concluding wrongly that the drug is better than placebo, while in fact there is no treatment difference and the observed difference is caused by chance. Otherwise there is a manufacturer risk (type II error, beta, which is the difference between unity and power) of discarding an effective drug by erroneously not detecting an existing difference between the new treatment and placebo, which is usually set to 20%. A larger sample size and a smaller variance will result in more extreme levels of statistical significance. Therefore the patient population should be made as homogenous as possible, such as by enrichment strategies, and the drop-out rate must be reduced

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in order to have sufficient evaluable patients. The cut-off value of $p < 0.05$ for the acceptable risk is somewhat arbitrary. There is no such value that is adequate to guarantee that a treatment effect truly does exist. Using 10% instead would decrease the necessary sample size to show a statistical difference and such a threshold might be more appropriate for orphan disease and the conduction of small trials. Using confidence intervals of estimates of the treatment effect may be more informative than *p*-values (CHMP/EWP/83561/2005).

As described above for adaptive trials, an interim analysis can be conducted during the course of a clinical trial. An interim analysis permits allocation of more patients to the more effective treatment as well as reduction of the study duration by early termination in the case of non-response or early emerging evidence of compelling treatment effects (and thus it also reduces the overall number of necessary study patients). Interim monitoring is especially useful when outcomes are observed faster than subjects will be accrued (i.e. walking period after 3 months of therapy observed in a study with 18 months accrual period). However, operational aspects such as who has access to unblinded efficacy data may be challenging as more complex decisions than those of the Data and Safety Monitoring Board must be made.

Drugs are approved based on their effect on clinically meaningful outcome and on patient benefit for reimbursement. In addition to efficacy and safety information for obtaining market approval, valid data on an orphan drug's effectiveness (see Chapter 7) are needed that may support claims for reimbursement by insurance health plans or public health systems such as in the UK. HTA trials may be assessed for this purpose. The term 'health technology' covers which methods, such as drugs, medical devices, medical procedures, etc., promote health, provide a cure for or prevent diseases.

HTA trials may be conducted for this purpose, which may answer questions such as whether the new drug works, for what patients, at what expense, and with what performance compared with other treatments. As treatment with orphan medicines tends to be expensive and resources of public budgets are limited, cost-effectiveness is an issue for discussion. Treatment cost per quality-adjusted life year (QALY) is used as a basis for comparison. However, cost-effectiveness is not the only justifiable basis for resource allocation, as equity and caring should also be valued (Burls et al. 2005; Sheehan 2005). Absence of an alternative therapy for a life-threatening disease against the high cost-effectiveness ratio of orphan drugs and comparatively weak clinical data must be balanced (Simoens and Dooms 2011). Resource utilisation does not include only the pure treatment costs for the drug under question, but also avoidance of hospitalisation, surgery or day care. There are doubts whether standard methods of HTA are adequate for decision-making towards funding of orphan drugs (Drummond et al. 2007). Other authors argue that valuing health outcome more highly for rare conditions is incompatible with other equity principles and theories of justice and the cost-effectiveness of orphan drugs should be treated in the same way as for other technologies (McCabe et al. 2005). Moreover, as drug reimbursement requirements are different between countries, regulatory authorities may be more or less willing to accept non-traditional models for demonstrating effectiveness to approve reimbursement. Providing data on cost-effectiveness through pharmacoeconomic trials is not possible with low patient numbers affected by rare diseases. Therefore, these data are generally provided in the post-marketing phase by means of real-world data derived from patient registries for orphan drugs (see section 6.4). Systematic reviews of the clinical effectiveness and cost-effectiveness of enzyme

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replacement therapies for Fabry disease and Gaucher disease have been published in the UK (Connock et al. 2006a; Connock et al. 2006b).

Nevertheless, there are still no satisfactory methods in place to measure the socio-economic burden and the health-related quality of life of patients with rare diseases. The BURQOL-RD project was initiated in the EU in 2010 as a 3-year research project under the 2nd Programme of Community Action in the Field of Public Health and aims to study ten rare diseases in different European countries (cystic fibrosis, Prader-Willi syndrome, haemophilia, Duchenne muscular dystrophy, epidermolysis bullosa, fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis Still, histiocytosis).

6.4 The need for long-term collaborative effort in collecting real-world safety and effectiveness data

Given the unmet medical need for treatment of many life-threatening rare diseases, drugs should be available for patients as early as possible. Full assurance that benefits outweigh the risks is not possible with short studies in a small group of patients.

Though the studied population relative to the total population affected with a specific rare disease may be higher than with common diseases, clinical studies are underpowered to detect adverse reactions of low frequency. Moreover, the 'real-life' patient population taking additional drugs may be more susceptible than pre-selected groups of study patients. Efficacy may have been established on biomarker endpoints

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and information on direct patient benefit or health-economic effects may not yet be available.

Therefore many orphan drugs are conditionally or under exceptional circumstances approved with post-marketing obligations for the manufacturer to further establish the safety and long-term benefit of the new treatment. Typically, the safety and effectiveness of an orphan drug in the post-marketing phase is demonstrated through registries.

Providing data to drug registries requires support by prescribing physicians and individual patients. As these registries are product-specific, data on a rare disease population gets divided into separate databases if several drugs are approved for the same disease and may evolve into mere marketing tools. This situation will not benefit the rare disease community and the development of disease-specific registries has been proposed as an alternative (Hollak et al. 2011).

Patient registries used to assess the effectiveness and safety of drugs in the post-approval phase require stringent quality standards and more detailed information on the clinical course than those established for epidemiological or public health purposes.

Amongst other sources such as an administrative claims database, surveys and medical records, patient registries provide a comprehensive basis for extracting real-world data. They describe drug effectiveness as an observed benefit for an individual patient under daily practice conditions. Both the Association of the British Pharmaceutical Industry (ABPI 2011) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Garrison et al. 2007) provide guidance on how to generate robust real-world data. This information may be used for value-based pricing and payment decision-making.

Reliance on observational studies based on patient registries presents some unique challenges. One problem is an inherent

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bias of patients enrolled in patient registries. Patients who are not on the new therapy are generally under-represented, and patients with more severe disease are usually over-represented (Clarke and Hernberg-Stahl 2010). The bias is minimised by establishing a relevant patient registry before a new drug is commercially available by general prescription.

A publication of the US Agency for Healthcare Research and Quality (Gliklich and Dreyer 2010) gives comprehensive guidance on how to implement a patient registry. Completeness of case ascertainment, high quality clinical data, verification of data validity and follow-up is mandatory (Richesson and Vehik 2010). A system of quality assurance must be implemented as otherwise data may not be adequate to support regulatory purposes. Complete clinical data may not always be entered into the database. Provisions must be made that definitions of disease-related events are consistently used by physicians. Laboratory tests are usually not comparable between hospitals.

In China, the development of the first rare-disease registry was started in May 2010, by the China-Dolls Care and Support Association, which is a patients' advocacy group mainly for those with osteogenesis imperfecta (Zhang et al. 2011).

Several examples of industry-maintained registries exist: Genzyme maintains a Fabry Registry (*https://www.lsdregistry.net/fabryregistry/*), a Pompe registry (*https://www.registrynxt.com/Pompe/Pages/Home.aspx*), a Gaucher registry (*https://www.registrynxt.com/Gaucher/Pages/Home.aspx*) and a MPS I registry (*https://www.lsdregistry.net/mpsiregistry/*). The Fabry Outcome Survey (FOS) by Shire Human Genetic Therapies is another example (Hernberg-Stahl 2006).

Another challenge of long-term, longitudinal, observational studies based on patient registries is the difficulty of achieving complete data capture and correct information entry (Clarke

and Hernberg-Ståhl 2010). Thus after some years of experience with the FOS, measures had to be introduced to improve the completeness of data capture (Clarke et al. 2011). Experience shows that data capture by registries focused on a relatively small set of particularly relevant core variables is, in general, better than that achieved by registries attempting to record a large number of variables.

A complementary research method is to conduct well-designed observational studies, which can be a valuable and effective approach to determining associations between specific exposures and outcomes (Concato et al. 2000; Vandenbroucke 2004; Vandenbroucke 2008). Observational studies are also considered as an alternative study design to solve some ethical dilemmas posed by parallel group studies with patients suffering from life-threatening diseases (Truog 2005). Inclusion criteria in observational studies are often broader compared with randomised clinical trials. Patients are representative for drug usage under clinical practice conditions as participants have a wider spectrum of coexisting illnesses, disease severity, and concomitant treatments. The number of recruited patients in observational studies is typically much higher than in interventional trials. Selection bias is the most important disadvantage of observational studies. It may be possible that untreated patients have less severe disease. Case series in a group of patients are the simplest observation studies. Cross-sectional studies, such as surveys and chart reviews, study exposure and associated outcomes. Case-control studies compare the frequency of events in exposed patients and matched non-exposed controls. In cohort studies, the presence of specific exposures is ascertained within individuals who are free of the outcome of interest, and incident events are evaluated from that point forward.

Database studies involve the analysis of the relationship between exposures and outcomes based on patient data from

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a registry. There are three types of clinical research databases (Kahn 1999):

- protocol-oriented research databases, used in large randomised controlled clinical trials;
- practice-oriented medical record databases, such as electronic medical record systems, which are more informal;
- databases that combine features of protocol-oriented and practice-oriented databases.

The goal of these databases is to create a large and diverse source of prospective longitudinal patient data. Databases that fall into the third category are usually multinational and multicentre, and record data over several years of clinical practice. Data from large outcomes databases can be used in several types of observational study, including cross-sectional, case-control and cohort studies (Thadhani 2006).

Different data standards (e.g. CDISC, ICD 10, ATC codes, Snomed) pose challenges for linking different patient registries. Epirare with various working parties wants to create standards for the collection of data within the EU (*www.epirare.eu*). With a similar goal, the US ORDR has launched a pilot programme to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR) (*www.grdr.info*).

Given the large number of patients available in the database, questions regarding drug efficacy in special populations and patient subgroups (e.g. females, children) may be answered, which normally would not be possible in the case of rare disease studies (Jones et al. 2011; Hoffmann et al. 2005; Hughes et al. 2011; Ramaswami et al. 2012). However, limitations introduced by selection bias should be kept in mind.

Two large patient databases that were used in the clinical outcome research of growth hormone give an idea about the degree of exposure that is built up in well-maintained international databases (Ranke and Dowie 1999): KIGS (Pfizer International Growth Database) was established in 1987 and now contains paediatric patient data from approximately 80 000 patients from over 52 countries. KIMS (Pfizer International Metabolic Database) began in 1994 and contains data on about 13 000 patients from over 31 countries, equating to more than 30 000 patient-years. Approximately 5 years ago, the ACROSTUDY database was established to monitor the long-term safety and effectiveness of pegvisomant in patients with acromegaly (Luger et al. 2011).

As there are no surrogate markers for safety (Temple 1999), the generation of pharmacovigilance data is an important part of the post-marketing obligations and a legal requirement for all drugs including orphan medicines (US FDA 2011b; European Commission 2008 EudraLex Vol 9a). Also for the post-marketing surveillance of medications, registries have become an important tool in addition to dedicated drug-safety studies (Willis et al. 2012).

The US approval letter of Myozyme® may serve as a typical example of post-marketing obligations to provide additional patient data: the manufacturer had the commitment to complete a juvenile- and adult-onset Pompe disease study with 24 months extension, to complete a paediatric pharmacokinetic study, to design and implement a registry of patients with Pompe disease, to assess growth effects, to investigate immune tolerance, and to further explore the dosing interval. In addition, non-clinical studies were requested, such as a juvenile animal study and a full set of reproductive toxicity studies. As orphan drugs are expected to be administered chronically or for lifelong use,

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animal carcinogenicity studies are normally requested, but as these studies require considerable time and animal resources they are usually postponed until the post-marketing phase (e.g. carglumic acid; Carbaglu®). For some endogenous substances, carcinogenicity studies may be considered unnecessary (e.g. galsulfase; Naglazyme®), while for other drugs, public programmes may do the testing (e.g. pentosan polysulphate sodium; Elmiron®, National Toxicology Program).

6.5 Notes

1. A declaration from the FDA that an uncompleted Phase III trial, clinical endpoints, and statistical analyses are acceptable for FDA approval
2. ICH aims to set unified standards for approval of medicines in Europe, Japan and the US.
3. Compare: Moore v. Regents of the University of California (United States, 1990: 51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479); Greenberg v. Miami Children's Hospital Research Institute (United States, 2003: 264 F. Supp. 2d 1064; No. 02-22244-CIV-MORENO).
4. The Central Research Infrastructure for Molecular Pathology (CRIP), the concept for a pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), and the Organization for Economic Cooperation and Development (OECD) global Biological Resources Centres network are examples of transnational, European and global biobank networks (Asslaber and Zatloukal 2007).

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7

Market access procedures for orphan drugs

With additional contributions by Chris Wilson

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Abstract: This chapter describes the current state of the art, challenges and approaches for improving orphan drug access for patients. Disparate data requirements behind EU centralised regulatory approval and local drug reimbursement, coupled with scarcity of patients and lack of information surrounding rare diseases have produced challenges for patients, payers and legislators. Currently there is no centralised or uniform mechanism considering these facts, which has led to inconsistency in patient access to orphan drugs between European countries and, in some cases, between different regions within a country. Initiatives such as the Clinical Added Value of Orphan Medicinal Products Information Flow (CAVOMP IF) aim to identify approaches to streamline the processes, coordinate activities, make better use of available data, and ensure earlier interactions with payers within the drug development process, in order to help meet their requirements.

Key words: Health Technology Assessment, market access, CAVOMP, payers, reimbursement.

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7.1 What is meant by market – or patient – access?

In broad terms, this is the final stage in the development of an (orphan) drug and relates to whether a patient is able to receive treatment in a timely and reimbursed manner. This may be ahead of formal marketing authorisation in some cases. To recap, and as has already been discussed in earlier chapters, orphan drug development is a three-step procedure, with the first two steps being orphan designation and marketing authorisation, which both occur at the regulatory (centralised) level, for example with the FDA in the USA, and with the European authorities – the EMA and the European Commission – in Europe.

However, the final step occurs at the payers' level, which in Europe is at the national or regional (local) level, and in the USA is at the level of the Health Maintenance Organizations (HMOs). HMOs are organisations that provide or arrange managed care in liaison with healthcare providers (e.g. hospitals, doctors) on a pre-paid basis, through insurance contributions.

For a drug to obtain marketing authorisation, regulators examine the properties of the drug to determine whether it has been shown to be safe and effective in the defined patient population as reflected in the clinical studies conducted, and whether, under the specified conditions of use, the benefit–risk ratio to the patient is favourable.

On the other hand, payers need to consider whether it is worthwhile paying for the drug, given the complexities of reimbursement, together with the limited budgets often available. Several health-economic models have been developed to help decide whether the additional clinical benefit of the new drug, when compared to available treatment, is: 1) worth paying for and 2) affordable.

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Payers have taken different approaches to finding answers to these questions, including the use of HTA methodologies. One approach is to perform an assessment of value for money by comparing the incremental costs of the new technology (with respect to relevant existing technologies) with the incremental benefits. Incremental benefits are normally defined in terms of health gain, either by use of a generic measure such as the QALY, or by use of a relevant clinical outcome for the disease area concerned (Hughes-Wilson et al. 2012).

Given that there is a centralised process for the authorisation of drugs and a decentralised process for pricing and reimbursement decisions, it is not surprising that there are differences in patient access to new treatments between Member States in Europe. This applies for both orphan and non-orphan drugs, but the combination of higher price points and smaller datasets for orphan drugs can tend to amplify the challenges for orphan drugs.

In some EU Member States, reimbursement is provided on approval, whereas in others, the procedures might take up to 4 years, while requiring the company to provide the product on a compassionate use basis in the meantime, due to the serious nature of the diseases to be treated.

This process can be even more complicated in Europe in that some countries, for example Sweden and Spain, have devolved responsibility for healthcare provision to the regional level, meaning that there are also differences between different parts of the country when it comes to access to healthcare including drugs.

In the USA there are differences between the various insurance plans offered by the HMOs and between different drugs depending on insurance coverage.

In addition, the specific situation for orphan drugs (only small cohorts of patients available to participate in clinical

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trials combined with high unmet medical need) can lead to the granting of a conditional marketing authorisation. This must be renewed on an annual basis and may involve post-approval commitments to generate additional data (often obtained through setting up registries to capture patient outcomes). These commitments by the company are agreed with the regulatory agencies and are used to gather additional information about a medicine's safety, efficacy or optimal use. This route to market is expected to become more common given the requirements of the new EU Pharmacovigilance legislation.

However, in most countries in Europe, the national HTA processes are not adapted accordingly, which leads to orphan drugs not fulfilling payers' criteria for reimbursement of the drug. This is partly related to the high price of these products, but is also due to the difficulties in demonstrating the clinical added value of the treatment. This has led to various initiatives from both government and patient advocacy groups to develop new health economic models for orphan drugs.

Another issue is that, when designing clinical trials for orphan drugs, manufacturers have traditionally not considered the payers' needs in terms of data requirements, notably the value of the product, or that the data required by regulators was not necessarily that required by the payers, in order to show the value of the product. Thus the criteria and the willingness to pay for a new treatment should be taken into account much earlier in the development process than has been done previously. One of the aspects of the proposed CAVOMP process would be to have earlier interactions between payers and the developers of a new drug to ensure adequate and appropriate data are generated. This is discussed in more detail in page 286.

Another aspect that influences the willingness to pay is that total healthcare costs are increasing and figures that cause concern for the years to come are presented, for example OECD Health Data. The economic crisis in the Eurozone has required stringent approaches to public spending and this, inevitably, impacts healthcare along with other government-regulated expenditures.

However, the figures for orphan drugs need to be put into context, because although the costs for orphan drugs can be substantial per patient, as a class and individually, they have a limited impact on the total healthcare budget, due to the low numbers of patients. For example, the cost was determined to be approximately 2% of the total hospital drug expenditures in many European countries in 2009, although it is predicted to stabilise at around 4–5% of the total pharmaceutical spending in Europe by 2020 (Schey et al. 2011).

However, payers' concerns can be understood on examining the figures without commentary. According to reported figures (Scrip 2012), 33 new products had their first market launches in 2011, which represented an increase over the average of 29 new products for the previous 10 years. More than one-fifth of the products were approved for rare diseases; therefore, it can be seen that this is an area of special interest to the pharmaceutical industry.

With an estimated 5000–7000 rare diseases, many payers are expecting a 'surge' of new drugs to treat these diseases to come to market over the next few years and are considering adjustments in their criteria for reimbursement accordingly. For example, expensive drugs such as Glivec® (imatinib) with several new orphan indications approved over the years have resulted in payers using a more conservative way of evaluating the value of new drugs. Another example is 3,4 Diaminopyridine (3,4 DAP) for the treatment of Lambert

Eaton Myasthenic Syndrome. Before a licensed product was available in the UK, 3,4 DAP (base form) was widely used. This product should have been replaced by hospital pharmacies when the licensed product Firdapse (3,4 DAP phosphate form) became available, but because of significant price differences, UK Primary Care Trusts took the unusual step of formally stating that 3,4 DAP (base form) will continue to be used.

The following is extracted from the West Midlands Commissioning Policy WM35:

The Primary Care Trust has adopted this policy that

> *it is satisfied that similar clinical benefits will be provided for LEMS patients by 3,4 DAP(base form) and by 3,4 DAP(phosphate form) (Firdapse®) but that the additional costs of prescribing the licensed drug, 3,4 DAP(phosphate form) (Firdapse®) cannot be justified given the opportunity costs of investing those sums in other areas to deliver healthcare benefits for the local population.*
>
> (*www.devonpct.nhs.uk/Library/Treatments_commissioning_policies/Policy%20-%20Firdapse%20-%20WM35%20-%20Dec%20LCCBs.pdf*)

In general, the price of a drug and the corresponding cost-per-patient are determined by the size of the patient population requiring therapy (in other words, the rarity of the treated disease) and by the risk taken to develop the product, which is reflected in the potential return on investment. It can therefore be seen that higher-risk projects, such as research into rare diseases and orphan drugs, will likely require higher potential return on investment to find enough investor support, which results

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in a higher cost to the patient. Unfortunately, this means that many patients may not be able to afford to pay for these drugs from their own funds and an assessment regarding reimbursement has, therefore, to be made to examine the impact of reimbursement on healthcare system budgets.

If payers are not prepared to reimburse treatment this could have a serious negative impact on patient access to much-needed drugs, and incentives provided to the pharmaceutical industry through legislation to promote the development of orphan drugs could be seen as a waste of money, which puts into question the concept behind orphan drug legislation.

In the case of smaller companies, the fact that they are not able to receive reimbursement for an orphan drug that they have invested in developing means they would be unlikely to recoup their investment and, thus, could run the risk of actually going bankrupt, or at least not becoming financially sustainable enterprises. If such companies have received incentives from the EU authorities or the FDA, this situation would create the risk that this invested public money may not achieve its objectives of delivering a treatment to patients.

Addressing the differences in patient access to treatment for rare diseases has been high on the political agenda for several years in Europe as reflected in key policy documents, including: the outcomes of the High Level Pharmaceutical Forum in October 2008, the European Commission Communication on Rare Diseases in November 2008 and the Council Recommendation on Rare Diseases in June 2009. This has been supplemented by building EU-level awareness and expertise on orphan diseases through EUCERD, and the development of National Plans for Rare Diseases (see Chapter 5).

7.2 Market approval versus market access

7.2.1 Europe

All drugs designated with orphan status must be assessed through the centralised procedure conducted at the EMA. The assessment is carried out by members of the CHMP against the same basic standards as non-orphan products, that is quality, safety and efficacy and, assuming that a positive risk–benefit ratio for the patient has been demonstrated, the orphan medicinal product may be finally approved by the European Commission.

After the Marketing Authorisation has been granted, orphan and non-orphan drugs must go through further pricing and reimbursement processes at the national level.

Many countries and/or regions use a HTA to help them in this decision-making process. Depending on the country, this assessment may not only be related to the clinical effectiveness and cost-effectiveness of a therapeutic solution, but may also consider the societal, organisational, legal and ethical implications of reimbursing a given health technology – be it a drug, or other therapeutic approach, including best supportive care. The HTA practices in Member States reflect individual healthcare and political environments, with differing mandates, funding mechanisms and policy, and this has resulted in a diversity of decisions on the approaches to healthcare technologies amongst Member States.

The purpose of the EU's orphan medicinal product legislation was to create a framework for the research, development and placing on the market of products in order to provide treatments for patients with rare disorders, on equal terms with other patients. This model has worked well

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and a number of drugs have received approval by the European Commission.

However, the EU's centralised authorisation process does not automatically provide patient access to treatments, and this post-authorisation element of the process, particularly in the case of orphan drugs, can be challenging. Receiving EU authorisation does not necessarily mean that the drug has actually been launched and made available to patients in all Member States.

Pharmaceutical market access strategy thus needs careful planning, including addressing reimbursement issues early in the development process, to maximise the chance of a successful outcome (see Chapter 6).

Although EU Member States have developed, and continue to develop, comprehensive strategies and/or national plans for rare diseases, including, for example, improving patient diagnosis, establishing patient registries and Centres of Excellence, and empowering patient organisations to assist in driving the process, it will be important to ensure that these measures contribute concretely in addressing challenges between the central Marketing Authorisation and patient access to new treatments.

One of the challenges in securing patient access to approved orphan therapies is the difference in the requirements of regulators and the HTA and payers' bodies. For a drug to receive Marketing Authorisation, the regulators focus on clinical aspects, including mortality and morbidity. Validated surrogate parameters could also be accepted and there is an increasing interest in the use of biomarkers to act as indicators of clinical outcomes. The data used for the regulatory process are generated from randomised clinical trials, in particular phase III and non-inferiority for efficacy and safety and the decision for Marketing Authorisation is based upon a positive benefit–risk ratio (efficacy and safety).

However, the Member States' HTA bodies and payer authorities are also interested in the in-life value of a given treatment. This means that their data sources go beyond those used for the regulatory processes. This includes approaches such as observational studies, post-marketing data meta-analysis from different sources and relative cost-effectiveness analysis. Direct and indirect costs as well as, in some countries, budget also impact the decision-making process. For orphan drugs / rare diseases, data are often very limited, especially if the HTA bodies try to find an authorised comparator.

One aspect of orphan designation and approval in Europe is that the manufacturer needs to be able to show that a treatment provides a unique or significant benefit. However, the available evidence at the time of marketing authorisation is normally based on a small number of patients included in clinical trials, which are not always placebo controlled, which, in turn, is a challenge when it comes to HTA.

Orphan medicinal products are often approved early on in their development, when compared with non-orphan drugs. As a result of the small dataset (limited clinical trial populations) approval is likely to be on a conditional basis, so there are often requirements to continue collecting information post-authorisation, for example via patient registries. This approach to authorisation coupled with follow-up measures to capture information on in-life outcomes is also in-line with the proposed CAVOMP process on information gathering and exchange.

Also, because of small patient numbers, the epidemiology of rare diseases is less well understood, making the projection of long-term benefit, beyond the end of the trial, or from surrogate markers to final clinical outcomes, more speculative. This greatly increases the uncertainty facing the decision-maker when considering orphan medicines.

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High-quality evidence on the clinical added value of orphan drugs is, therefore, rarely available at the time the marketing authorisation is granted, and there is often a lack of understanding of the true benefit of the product when given outside a trial environment (i.e. in 'real life'). By capturing data into patient registries, not only can post-drug approval commitments be fulfilled, but also knowledge about the rare disease and its optimal treatment can be collated (see Chapter 6).

As has already been mentioned, the reimbursement of orphan drugs is not regulated at the EU level as this is not addressed by the EU Regulation on Orphan Medicinal Products and is outside the scope of the EU competence – the provision of healthcare remaining a Member State responsibility. Reimbursement is, therefore, a national responsibility and the national procedure for reimbursement in the 27 Member States is handled by 44 regulatory agencies. There is no harmonisation of the evaluation, and different approaches are used. With the small number of patients included in clinical trials, the conclusion on a national level is often that there are not enough data to make any decision about reimbursing the drug.

Policymakers and healthcare payers are, today, increasingly using HTA, including economic evaluations and budget-impact analyses, for reimbursement decisions. National pricing and reimbursement regimes vary significantly among Member States, although initiatives to facilitate understanding and shared approaches to evaluations that may be carried out in different countries have been explored in recent years, for example EUnetHTA launched by the European Commission.

Despite this increase in coordination and cooperation, the heterogeneous approaches in the different countries make patient access to orphan drugs complex.

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The reimbursement decision-making process has not always been adapted so far to the specificities of orphan drugs, and conventional HTA methodologies are not always adapted for these drugs. The price-per-patient may make it almost impossible to prove cost-effectiveness for some products, and orphan drugs are not made available in all countries on the same basis.

7.2.2 USA

In the USA, the process for drug market approval and safety assessments are conducted centrally at the FDA, and in general the FDA focuses on Phase 3 placebo-controlled trials as the gold standard of evidence, as opposed to head-to-head trials against the most appropriate active comparator.

However, an analysis of cost-effectiveness is outside the remit of the FDA, and, as in Europe, formal technology assessments are conducted locally. The funding for and use of health technology assessment programmes in the USA is fragmented and uncoordinated, and includes both public and private sector initiatives. The Medicare and Medicaid programmes are the largest government-sponsored purchasers of healthcare in the USA.

The Agency for Healthcare Research and Quality (AHRQ) is the largest federal funder of publicly available health technology assessments in the USA.

The NIH does not have a programme for conducting health technology assessments, but will often conduct evidence-based reviews in the process of developing clinical practice policies for particular medical conditions.

The commercial health insurance market finances medical care services for more than 200 million individuals through diverse employer-sponsored and self-insured health benefits programmes. The five largest health insurers (Aetna, Cigna,

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Kaiser Permanente, United Healthcare, and WellPoint) cover or are responsible for more than 50% of all employer-sponsored members in the USA. Roughly 95% of all persons with drug coverage will receive pharmaceutical benefits through Pharmacy Benefits Management (PBM). The four largest PBMs (Caremark, Medco, Express Scripts, and WellPoint NextRx) process nearly 70% of the 3 billion prescriptions dispensed annually. Many private insurers and PBMs have sizeable HTA programmes staffed by qualified clinical experts and financial analysts and are supported by sophisticated data systems.

In the USA, payers do not have a separate reimbursement process for orphan drugs, and payers traditionally have not put any major restrictions on these drugs.

As with other non-orphan drugs, many payers are now passing more of the cost burden to patients by increasing the co-insurance or by moving products to the pharmacy side where the patients share more of the cost burden. Payers are also starting to manage expensive orphan drugs in the pharmacy channel, by placing them on the fourth tier with high co-insurance, thereby limiting access.

Patient-assistance programmes are a resource for many patients in the USA. The amount of financial assistance varies based on individual patient income and may involve other organisations. Genzyme Corporation, for example, offers the Charitable Access Program for patients using imiglucerase (Cerezyme®) for the treatment of Gaucher's Disease, laronidase (Aldurazyme®) used in ERT for mucopolysaccharidosis, agalsidase beta (Fabrazyme®) in Fabry disease, and alglucosidasealfa (Myozyme®) for treatment of Pompe disease. These programmes offer free drugs in limited amounts to qualified patients.

Other programmes, such as that offered and administered by NORD, assist insured patients with insurance premiums and co-payments. On its website, NORD lists different

patient-assistance programmes that it administers on behalf of orphan drug manufacturers (*http://rarediseases.org/*).

7.3 Differences in access procedures for orphan drugs by country

When introducing a new drug onto the market it is important that the pharmaceutical company understands the role and expectations of all the different stakeholders involved in the access process.

National payers have often received a budget that they need to manage for all drugs – orphan and non-orphan, although, in some countries, there might be a special budget for rare diseases. In both these cases, payers will be very concerned that they are receiving value for money. Payers will also frequently have to address national (regional) healthcare policy priorities.

A further balance that is required is that, whilst regional and local payers have to keep their spending within budget while providing the best health outcomes for the regions they are responsible for, physicians may not have a direct connection with the cost implications of the actions they take in providing the best quality care for patients, and patients may be interested in getting access to the best treatment available, whilst paying as little as possible for the treatment, although to put this into context, not all orphan drugs are equally expensive, and this dichotomy holds true for both orphan and non-orphan disease.

The financial environment has changed a lot since the introduction of the orphan drug legislation and in the current cost-constrained situation, payers also have the perception that they are about to face an 'avalanche' of orphan drugs coming to the market, stimulated by the incentives and

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the interest of an increasing number of companies entering the field.

The likelihood of this avalanche and a resulting high cost impact might not be totally accurate: the majority of these anticipated new drugs are likely to be oncology products, although not all of them are for first-line treatment (so a patient must have failed treatment with another agent before receiving the new drug). On the other hand, a second large percentage (about 25%) of the expected new drugs are intended to treat metabolic diseases, and the nature of these diseases means that there is a potential for lifelong treatment.

However, this must be put against the background of the rare disease sector as a whole. Not all of the patients are diagnosed and, even if they are diagnosed, not all of them will be treated. Payers also fear that companies are 'using the system' and are 'salami-slicing' indications into multiple subsectors – a fear that is increased by the increased focus on so-called 'personalised medicine', where a condition could, for example, be subdivided into different forms on a genetic basis. Payers therefore question whether they are going to be able to pay for all these new orphan drugs and why they should pay premium prices.

For all these reasons, there continues to be increased scrutiny of orphan drug access from the payers' side, although predicting the future needs for orphan drugs by using the number of drugs with an orphan designation and the currently available incidence figures might not be the most accurate estimation.

7.3.1 Is it worth paying for the added clinical effect offered by orphan drugs?

On the one hand, due to the low number of patients that may possibly be treated with an orphan medicinal product,

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the impact of these products on the healthcare budget is generally limited, although on the other hand, with a large number of rare diseases, the total budget impact may be considerable (Heemstra 2010).

To better understand the problem, Schey et al. (2011) have estimated the projected budget impact of orphan medicines in Europe over the period 2010–2020, expressed as a percentage of total European pharmaceutical expenditure. They created a disease-based epidemiological method based upon trends in the designation and approval of new orphan medicines, prevalence estimates for orphan diseases, and historical price and sales data for orphan drugs in Europe (defined as Eurozone + UK). First, they predicted the number of diseases for which new orphan drugs will be approved over the next decade, based on an analysis of trends from the EU registry of orphan medicines; thereafter, they estimated the average ex-factory drug cost across an orphan disease life cycle, from the year in which the first orphan medicine is launched to the point where the first medicine loses market exclusivity.

The results from the model predicted a steady increase in the cumulative number of diseases for which an orphan drug is approved, averaging just over five new diseases per year over the next 10 years. The share of the total pharmaceutical market represented by orphan drugs is predicted to increase from 3.3% in 2010 to a peak of 4.6% in 2016, after which it is expected to level off through 2020 (Schey et al. 2011) as growth falls into line with that seen in the wider pharmaceutical market.

The conclusion was that, although European orphan drug legislation has led to an increase in the number of approved orphan drugs, the growth in cost, as a proportion of total pharmaceutical expenditure, is likely to plateau over the next decade as orphan growth rates converge. Based on these

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results, the authors concluded that fears that growth in orphan drug expenditure will lead to unsustainable cost escalation do not appear to be justified.

One of the challenges in predicting the true impact of a new treatment on the healthcare budgets is that there are challenges in finding all patients that are in need of the new treatment. This low disease awareness affects referral and diagnosis of patients with rare diseases, and there is a need for communication about the disease itself and the existence of any new treatment. Due to the frequent lack of knowledge surrounding orphan diseases, often there is no optimal disease management, and there is a need for improved treatment guidelines to improve patient management, and if possible, secure cost-effective treatment.

Other challenges experienced by payers of orphan drugs are discussed in an article by Hughes-Wilson et al. (2012), in which the authors provide a possible way forward for the evaluation of orphan drugs based on multiple criteria including rarity, level of uncertainty, manufacturing complexity, disease severity, available alternatives and level of impact on condition / disease modification.

7.3.2 Europe

Each country makes its own decisions on the pricing and reimbursement of orphan drugs. If payers think the budget impact will be too high or that they are not getting appropriate value for money according to their national assessment procedures, they may restrict the reimbursement of new orphan drugs to subpopulations of patients or even deny or withdraw reimbursement.

In order to ensure that the drugs are being used appropriately and that patients are being accurately diagnosed and treated, several countries have established

specialised centres. This also enables the healthcare systems to monitor the use and outcomes of and reimbursement for the treatments.

France

Patients diagnosed with rare diseases must attend a 'Centre of Reference'. Specialists at these centres confirm diagnosis before the patient can receive often high-priced orphan drugs.

Italy

'Rare Disease Centres' are the only official centres allowed to prescribe orphan drugs. These centres collect efficacy and safety data relating to products used; they also enable the tracking of any indication restrictions placed on these products.

UK

NHS National and Regional Commissioning / Specialised Commissioning from NHS Specialised Services:

> *NHS Specialised Services is the national organisation responsible for the commissioning of specialised services that help improve the lives of children and adults who have very rare conditions.*
>
> *Commissioning in the NHS is the process of ensuring that health services meet the needs of the population. It is complex and includes assessing the needs of the population, selecting health care service providers and ensuring that these services are safe, effective, patient-centred and of high quality.*
>
> *(www.specialisedservices.nhs.uk/info/nhs-specialised-services).*

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In England, there are ten Specialised Commissioning Groups (SCGs) that commission specialised services for their regional populations, which range in size from 2.8 to 7.5 million people. The National Specialised Commissioning Group (NSCG) facilitates working across the ten SCGs at a regional and supra-regional level.

Commissioning at a national level

About 60 highly specialised services are commissioned nationally by NHS Specialised Services. Generally speaking, these are services that affect fewer than 500 people across England or involve services where fewer than 500 highly specialised procedures are undertaken each year.

The Advisory Group for National Specialised Services (AGNSS) was until recently a committee that advised health ministers on which services should be nationally commissioned and the centres that should provide them.

New technologies

The remit of AGNSS was to consider a small number of highly specialised new drugs and technologies. AGNSS's role was to make recommendations to ministers about whether the drugs and technologies it considers are appropriate for commissioning at a national level. However, as a result of the NHS Commissioning Board (now known as NHS England) assuming responsibility for commissioning specialised services in April 2013, AGNSS has now been disbanded (Adams 2013).

The role that AGNSS played (assessing drugs and technologies that NICE (the UK HTA body) decided were not suitable for their appraisal because of the very small patient numbers involved) will now be brought under the control of NICE. This has caused debate as to whether the models NICE currently use to determine value, including

their QALY-based approach, are appropriate to consider these specialised products. However, it is still too early to comment on whether the involvement of NICE in the assessment of these ultra-orphan drugs will ultimately be of benefit to rare disease patients (Adams 2013).

One example where the use of new technologies is helping patients is in the Centres that were previously appointed by the NHS Commission to treat the following lysosomal storage disorders: Gaucher's disease, Anderson-Fabry's disease, Mucopolysaccharidosis type I (MPSI, which occurs as Hurler's syndrome, Hurler-Scheie syndrome and Scheie syndrome), Mucopolysaccharidosis type VI (MPS VI or MaroteauxLamy syndrome), Pompe's disease, Mucopolysaccharidosis type II (MPS II).

There are currently eight nationally designated centres that are funded to prescribe treatments for these diseases, although it is important to note that only treatments that are licensed and for the indications named in the licence will be funded.

Germany

The assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) is taken into account by the German Joint Federal Committee G-BA, which makes the final decision on the added value of products under the early benefit assessment procedure.

Esbriet® (pirfenidone) for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) was the first orphan drug to be reviewed by IQWiG since new healthcare legislation known as AMNOG was enacted in January 2011.

As for other orphan drugs, the marketing authorisation was obtained centrally through the European procedures, including EMA assessment, but the IQWiG concluded that

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no additional benefit could be found for pirfenidone. However, under German law, orphan drugs are deemed as having an additional benefit, due to the fact that they need to demonstrate this in the authorisation process. This led IQWiG to assess the Esbriet® additional benefit as a given, but not quantifiable.

It is also instructive to consider a much more recent case (May 2012) of Benlysta® (belimumab for the treatment of systemic lupus erythematosus). The IQWiG reviewed the data and, although it noted that data from two pivotal trials had been submitted and were sufficient to show effectiveness for drug approval, they were not appropriate to show added benefit (no comparison with optimised standard therapy).

A similar situation exists in the UK, following a review of the same drug by NICE (the UK HTA), who rejected Benlysta® stating that although there was evidence of its clinical effectiveness, its cost–benefit ratio was too high.

7.4 Availability and access to orphan drugs

As discussed earlier in this chapter, regulatory marketing authorisation does not necessarily guarantee patient access to any given drug. This is particularly true for higher-cost therapies, including some orphan drugs, because access in the different international markets depends primarily on reimbursement policies and prices, and to a lesser extent (in Europe) on co-payments.

Blankart et al. (2011) conducted an international comparison of pharmaceutical treatments for pulmonary arterial hypertension (PAH), Fabry disease (FD), hereditary angioedema (HAE) and chronic myeloid leukaemia (CML)

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and studied the availability of, and access to, orphan drugs. They looked into differences in the availability of orphan drugs and in patient access to them in 11 pharmaceutical markets: Australia, Canada, England, France, Germany, Hungary, the Netherlands, Poland, Slovakia, Switzerland and the USA. Indicators for availability were defined as (i) the indications for which orphan drugs had been authorised in the treatment of these diseases; (ii) the application date; (iii) the date upon which these drugs received market authorisation in each country. Indicators of patient access were defined as (i) the outcomes of technology appraisals; (ii) the extent of coverage provided by healthcare payers; (iii) the price of the drugs in each country.

The broadest range of indications was found in Australia, and the largest variations in indications were found for Pulmonary Arterial Hypertension drugs. Authorisation process speed (the time between application and market authorisation) was fastest in the USA, with an average of 362 days, followed by the EU (394 days). The highest prices for the included drugs were found in Germany and the USA, and the lowest in Canada, Australia and England. Although the prices of all of the included drugs were high compared with those of most non-orphan drugs, most of the insurance plans in the country sample provided coverage for authorised drugs after a certain threshold.

The authors concluded that although there were some variations between countries in availability and access to the orphan drugs studied, all were available and accessible. They found, however, that co-payments in the USA and Canada were important barriers to patient access.

A slightly earlier study, conducted in 2010, looked into the variations in access throughout Europe (Heemstra 2010). As has already been noted, reimbursement authorities across Europe use different criteria to assess the value of a new

orphan medicinal product and to determine reimbursement levels. Some countries, for example France, Italy and Spain, base their decision on the clinical efficacy, and no formal additional HTA process is needed, contrary to the requirements for drugs for non-rare indications. Alternatively, authorities in some other countries (the Netherlands, Sweden and the UK) base their decisions on the outcomes of HTA evidence.

Despite these differences in reimbursement systems, a report in 2010 by the Office of Health Economics (OHE) concluded that there generally was little variation with regard to reimbursement of the first 43 authorised orphan drugs between France, Germany, Italy, the Netherlands, Spain, Sweden and the UK (Mestre-Ferrandiz et al. 2010). In Scotland, where the Scottish Medicines Consortium evaluates all new medicines, out of 28 evaluated orphan medicinal products, 13 (46%) were not reimbursed. A lower number of reimbursed orphan medicinal products were also reported for Sweden. Although Sweden accepts a higher willingness-to-pay threshold for severe diseases, only 56% of potentially available products were reimbursed in Sweden. The following quotes are taken from OHE consultancy report of November 2010 (Mestre-Ferrandiz et al. 2010):

> *The application of HTA standard methodology to appraise orphan drugs can lead to high rates of rejection and significant delay to access to new OMPs.*
>
> *The increasing demand for HTA to inform health care decisions will therefore represent a major challenge in terms of access to OMPs, which are unlikely to meet HTA standard requirements.*

A study of the Belgian Health Care Knowledge Centre (KCE) compared the variations in access and based its

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findings on the first 47 authorised orphan drugs in Belgium, France, Italy, the Netherlands, Sweden and the UK (Denis et al. 2009). There was a variation in access ranging from 23 available drugs in Italy, 28 orphan drugs in Sweden, up to 35 in France and 36 in the Netherlands. Both the OHE and KCE studies reported that France and the Netherlands were the two countries that consistently reimbursed the most orphan medicinal products. This is also in-line with earlier findings by Drummond et al. (2007), although please note that the situation in the Netherlands is likely to change in 2013.

In these two countries rare diseases and orphan drugs are high on the political agenda. France was the first country to initiate a national plan for rare diseases. In the Netherlands, the Steering Committee on Orphan Drugs was set up to encourage the research and development of orphan drugs and to improve the management of rare diseases, although the Committee was disbanded in December 2012. Despite this, the Netherlands is, at least at the time of writing, one of the few countries that have a dedicated orphan drug reimbursement regulation that conditionally reimburses expensive orphan drugs when used in academic hospitals for a period of 4 years. During this period, the sponsor of the product on this list should conduct cost-effectiveness research in order to qualify for full inclusion on the list after 4 years.

The Health Care Insurance Board (College voor Zorgverzekeringen (CVZ)) is the council that advises the Dutch Ministry of Health on the results of the 4 years of cost-effectiveness research. In 2012, the results of the cost-effectiveness research of three orphan medicinal products for Fabry and Pompe disease on the Policy Rule Orphan Drugs were evaluated. At the end of November 2012, the CVZ gave advice to the Minister of Health to exclude these three

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orphan drugs from the add-on financing (and therefore also from the basic health insurance package). The CVZ also made the recommendation to create a new form of financing for these three orphan drugs (and potentially also for a limited group of other expensive treatments of rare conditions). The suggestion from the CVZ was that in this way it is possible to collect more data on the efficacy of these orphan medicines. However, at the time of writing, the Dutch Minister had still to take a decision on this advice from the CVZ (end of December 2012).

EURORDIS conducted a Survey on Orphan Drugs Availability in Europe (2007) that showed, in-line with the above studies, that there is an unequal access to orphan drugs in Europe and that access to orphan drugs is largely dependent upon the country in which patients live. The survey considered the 22 orphan drugs that had a market authorisation before 1 January 2006, and it included the 25 EU countries before the last enlargement, as well as Iceland, Norway and Switzerland. The survey addressed questions about dates of national registration and when the drug was first made available to patients, and of first sales and any reasons if it was unavailable.

The results showed that availability differed a lot between the different countries from those with most orphan drugs available to patients (20 or 21 orphan drugs) followed by an intermediate availability of 15 to 19 orphan drugs. The worst contenders at that time had only up to 4 orphan drugs available.

'This situation is not only inequitable because patient access to orphan drugs depends on the country where they live, but it is also totally unethical,' commented EURORDIS (*www.eurordis.org/content/improving-patient-access-orphan-drugs-europe*). They went on to explain that the 180-day legal delay for placing medicinal products on the

market is not respected, and orphan drugs are made available in a timeframe and under conditions of access that are worse than for other drugs, although they are intended for rare conditions where there are unmet medical needs.

EURORDIS performed another survey in collaboration with the National Alliances on Rare Disease in 2010.[1]

This time the availability of the 60 drugs with a marketing authorisation was examined and ten countries were surveyed. The response rate was 77% and the availability of the 60 drugs ranged from 10–30% in four countries, which the authors proposed could be due to lack of knowledge, information and transparency. In the remaining six countries the availability was between 70 and 90%.

There are several summary reports available on the different approaches used in the different European countries:

- 2011 EUCERD Report on the State of the Art of Rare Disease Activities in Europe: *www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf*
- EURORDIS – The Voice of 12,000 Patients: *www.eurordis.org/publication/voice-12000-patients*
- KCE Report 112C on 'Policies for Orphan Diseases and Orphan Drugs': *http://ec.europa.eu/health/ph_threats/non_com/docs/policies_orphan_en.pdf*
- The Belgian Plan for Orphan Drugs – 'Recommendations and Proposed Measures for a Belgian Plan for Rare Diseases': *www.kbs-frb.be/uploadedFiles/KBS-FRB/05%29_Pictures,_documents_and_external_sites/09%29_Publications/PUB_3011_BelgianPlanForRareDiseases2011_DEF.pdf*

Another study (Abraham et al. 2011) conducted in the USA by the National Bureau of Economic Research found that insurance coverage for chronically ill patients is less generous

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than for patients without a chronic condition, primarily due to higher cost sharing for prescription drugs. Economists at the University of Minnesota, University of Wisconsin-Madison, and Indiana University measured total out-of-pocket spending compared with total health spending and found that for households spending more than US$8000 per year, out-of-pocket spending was significantly higher in chronic disease households. The researchers conclude that 'it is benefit design, not differences in the types of plans covering the (chronically ill and non-chronically ill), that explains the difference we observe in insurance generosity . . . the specific services used most by the chronically ill – prescription drugs – are, by design, reimbursed at a lower rate.' Therefore, 'the weight of the evidence suggests that the current standard in insurance design of higher co-insurance for prescription drugs is worth reassessing.'

7.5 Difficulties in estimating the value of treatment

7.5.1 Small datasets, surrogate endpoints, non-routine clinical trial design, early approval

The most frequently asked question is: Why are patients not getting access to authorised orphan drugs? Numerous supplementary questions have also been raised: Is it due to rising healthcare costs, resulting in payers not being able to afford the treatment for often high priced orphan drugs? Is it due to the fact that payers perceive there will soon be a boom in new orphan drugs? Is it the 'Glivec effect', whereby the same drug receives multiple orphan drug designations/marketing authorisations? Or could it be related

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to the increasing use of Health Technology Assessments, whose methodologies might not have been adapted to orphan drugs? And one further question of relevance: How to measure the value of an orphan drug?

There are some specific features of developing treatments for rare diseases that create challenges for policymakers: due to the small number of patients suffering from a rare disease, the number of patients who might be eligible for inclusion into randomised clinical trials is limited. In addition, these trials are often difficult to conduct/design (for example, the use of surrogate endpoints and the increasing use of biomarkers – see Chapter 6) and an approval could be based on non-placebo-controlled clinical trials, something that can be discussed with the regulatory drug agencies (EMA or FDA) during the protocol assistance/scientific advice phase of the drug development programme.

Additional supporting data may come from individual observational studies, published case reports and opinions of experts or anecdotal reports. The small datasets and the challenges in gathering the necessary information to document outcomes in the same way that is possible for more prevalent diseases, coupled with the high unmet medical need, can lead to a perception that regulatory approvals for orphan drugs are, therefore, based on a less robust dataset compared to approvals of conventional drugs. Regulatory approvals may be given earlier on in the developmental phases of the programme and may be given on an exceptional or conditional basis, against a commitment to develop additional real-world data to prove long-term safety and effectiveness in a larger number of patients. As a result of the rarity of the condition, the quality and quantity of evidence on the clinical added value of an orphan drug are therefore often limited, when compared with more prevalent conditions.

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The design of clinical studies for drug approval does not, from the regulators' perspective, take the HTA aspect into consideration. However, there are opportunities for discussion with the HTA authorities in parallel with the regulators when designing clinical trials for orphan drugs. For example, there have been 12 joint scientific advice meetings with Pharma, EMA and HTA from Sweden, UK, France, Italy, the Netherlands, Spain and Germany.

In addition, in Sweden, the **T**andvårds och **L**äkemedelsförmånsverket (TLV, The Dental and Pharmaceutical Benefits Agency) (which includes The Board for Pharmaceutical Benefits, responsible for establishing rules on pricing and reimbursement for new medicines) and the MPA (the Swedish Competent Authority for the licensing of medicines) have implemented a permanent process of joint scientific advice.

This ongoing discussion between regulators and payers is an element that is considered necessary to address some of the potential data shortfalls and to increase understanding of the feasibility of conducting the studies from the earliest stages of drug development. It is also one aspect the proposed CAVOMP process will develop.

When considering how to assess the value of the new drug, which payers have to do when using the HTA approach, a comparator is often used which is frequently another conventional treatment, but this is something inherent in the definition of an orphan disease (disease for which no treatment has been developed because of its rarity) that is lacking.

Another comparator could be to compare treatment to the natural history of the disease, although again, these data are also often lacking. Before a treatment is available or under development, data are rarely collected in a structured way and the lack of diagnosis and/or of proper ICD coding makes

it difficult to find population-based information. Starting to collect natural history data early on in drug development will be valuable when comparing treatment effects (see Chapter 6). This could also provide both valuable information on disease progression and data on the burden of disease, although frequently the rarity of patients does not allow comparative analysis throughout all the stages of the disease progression.

Improvement in clinical outcomes is also difficult to estimate, especially when there is no valid model for the disease progression over time. Such a model is difficult to establish even when a treatment is available, especially given that the untreated population consists mainly of less severely affected patients. Should a model exist, the following question would then arise: What is an acceptable outcome for a progressive disease . . . slower disease progression or the stabilisation or regression to the norm of the disease?

In addition, the cost for additional health benefits is usually high compared to many non-orphan treatments; for example Kuvan®, the only medical treatment to lower blood phenylalanine levels in patients with phenylketonuria (PKU), was not reimbursed in Sweden due to it not being considered cost-effective compared to diet restrictions.

Drummond (2008) argues that there should be other factors (i.e. patient-reported outcomes such as social and QOL) than those involved in the traditional cost-effectiveness models used in HTA for orphan drugs. Diseases/conditions that are the subject of a designated orphan drug are, by definition, serious, often life-threatening conditions.

One approach to trying to establish a method for quantifying this is the BURQOL-RD study. This is a 3-year project, partially funded by the European Commission's DG SANCO, which commenced in April 2010. The objectives of the project are:

- to generate a methodological framework to measure the socio-economic burden of rare disease;
- to define a methodological framework to measure the health-related quality-of-life (HRQOL) of rare disease;
- to develop unified instruments to gather information on the socio-economic burden and HRQOL of rare disease throughout Europe;
- to perform a pilot study measuring the socio-economic burden and HRQOL for selected rare disease;
- to refine and package the tools developed for continued and more extensive costs and HRQOL studies of rare disease.

The project will thus generate a model to help quantify the socio-economic costs and HRQOL for both patients and caregivers for up to ten rare diseases in different European countries. The following diseases are being targeted:

- Cystic fibrosis
- Prader-Willi Syndrome
- Haemophilia
- Duchenne Muscular Dystrophy
- Epidermolysis Bullosa
- Fragile X Syndrome
- Scleroderma
- Mucopolysaccharidosis
- Juvenile idiopathic arthritis
- Histiocytosis.

It is expected that the outcome from this project will be an integrated and harmonised set of instruments to assess and

monitor the socio-economic burden and HRQOL of patients affected by rare disease and their caregivers. In addition, a detailed analysis of the services (health and social care) received by people with a specific rare disease in different EU countries, including the identification of formal and informal care, will be conducted.

A report on the current socio-economic and HRQOL status of rare disease patients and caregivers for the selected rare disease and EU countries will subsequently be produced, and it is hoped that the results and deliverables that emerge will stimulate the future comparability and monitoring of rare disease in Europe, as well as anticipate future information needs.

So from these, and other, projects it is anticipated that by including patient-reported outcomes early in drug development not only would clinical parameters be possible to collect, but also patient perceived health, QOL and social status related to school and work situations. Also, by looking beyond the conventional parameters normally included in HTA, it might be possible to obtain valuable information on health outcomes and to see the real difference the treatment makes to an individual patient and to groups of patients. This could help address the criticism that at present the cost-effectiveness of orphan drugs, especially those for very rare diseases, cannot be established with the standard methods used by HTA bodies to inform reimbursement authorities (Tambuyzer 2010).

7.6 Differences in patient access schemes and patient registries

Often in the past, industry – individual companies – have been requested to initiate registries as part of follow-up

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measures from the regulatory authorities as part of the marketing authorisation process (see chapter 6).

Patient registries designed to provide data for regulators have the advantage that the data entered are often validated at several levels. In addition, there is less confusion about the diagnosis/ICD coding, an issue for data on patients with orphan diseases collected by registries not driven by a specific disease.

As part of efforts to manage healthcare budgets as well as to understand the true contributions made by orphan – as well as some non-orphan – drugs different 'risk-sharing' programmes have been put into place in several countries to 'share the risk' between the payers and the manufacturer. These programmes can take a variety of forms, including finance-based schemes, as well as price–volume agreements or outcomes-based mechanisms.

An outcomes-based scheme could be based on conditional reimbursement, which will be evaluated on the generation of evidence over time. Another example is reimbursement with a guarantee of a given clinical outcome, that is, that payers are provided with the drug either for a defined period of time or number of treatment cycles, and manufacturers either refund the cost for patients not achieving the target outcome, or continue providing the drug free of charge for extra treatment cycles; or the payers buy the drug for lower than the regular price for the first treatment period, and then pay the full price for those patients achieving the target outcome.

For rare diseases where only limited knowledge is available on how the disease manifests itself, the collection of additional information on patient outcomes as part of a conditional reimbursement is the most common approach used by manufacturers to supplement efficacy data generated from randomised clinical trials. Indeed, some countries such

as France, the Netherlands and Sweden have introduced continuous re-evaluation of the benefit of treatment by orphan drugs for pricing and reimbursement purposes.

Patient registries are, therefore, often established as a method to capture the outcomes on which to base an evaluation of in-life outcomes. Often these are nationally based, especially if used to capture data for national pricing and reimbursement decisions. However, given the rarity of the conditions, registries on a European or global level, rather than on a national level, represent the optimal way to get a sufficient number of patients to gather datasets that are likely to be meaningful enough to satisfy regulatory bodies' and payers' requests on additional long-term outcomes data.

Patient registries can also be used to evaluate, identify or develop factors to be used as health indicators. For example, patient-reported outcomes have great relevance as an indicator for rare diseases, but only if validated questionnaires are used. These health indicators can serve as important tools to prospectively evaluate individual treatment outcomes.

Going forward, when industry initiates patient registries to meet the demands of regulators, it could be worthwhile to consider in the design of these studies the demands of the pricing and reimbursement agencies and their needs and demands regarding, for example, treatment follow-up. This would mean that within the pharma company, there needs to be cross-functional communication on regulatory and reimbursement demands, something that could be difficult when these different activities are frequently handled by different parts of the organisation.

Patient registries can provide data on long-term effectiveness and safety to pricing and reimbursement agencies in some countries. However, as previously indicated,

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data for a typical HTA are not as obviously straightforward for an orphan drug as for conventional drugs, and a patient registry will not change that fundamental difficulty. Better involvement of the pricing and reimbursement authorities in the earliest stages, and engagement with the HTA bodies to understand their requirements, could contribute to getting the most useful dataset out of the registries. This needs, of course, to be carefully coordinated with physician time, the existence of potentially competing registries and the weight/validity that data from industry-sponsored registries is afforded. There are several activities ongoing at the European level, as mentioned earlier, which are specifically aimed at addressing registries' issues for orphan drugs, with the intention of evaluating these combined challenges.

7.7 Patient involvement in HTA

7.7.1 Europe

There is increasing emphasis on providing patient-focused healthcare and ensuring that patient involvement is included in the design of health services. Having said this, patients' perspectives about their illness are not always directly included in the health technology assessment process, although the robustness and validity of HTAs can be strengthened by including this information, and also by actively engaging patients in the HTA process.

However, patient involvement in the HTA processes in many countries is still in its infancy, even though many patients' organisations have expressed a desire to be more meaningfully involved in the processes. At the same time, very few HTA agencies currently involve and integrate patients' perspectives in their reports, although feedback

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from the HTAs indicated that they would ideally like to improve patient involvement in the first phases of HTA.

The main results of an interim report from a survey conducted by the EPF (the umbrella organisation of pan-European patient organisations active in the field of European public health and health advocacy) with HTA agencies in Europe between November 2010 and February 2011 are now available. Please see *www.eu-patient.eu/Initatives-Policy/Initiatives/* for further information.

They report that, from the 40 out of 50 HTA agencies that completed the survey from 23 Member States, the type and level of patient involvement is diverse, which is a reflection of the different rationales, motivation and approaches of the HTA bodies within the different countries.

To promote patient involvement, HTAs need to improve means of facilitation and engagement, such as education and training programmes, holding public conferences, seminars and workshops, in addition to providing easy-to-read HTA summaries. This would enable patient organisations to better understand the principles of HTA and, thus, be more proactive in identifying ways and means to get involved in a constructive manner at the right time within the different national processes. Above all, patients' organisations have to be vigilant and flexible to rising opportunities. They have to demand transparency in decision-making and a legal framework for patient involvement in HTA.

Patients' organisations have been playing an active role in preparing themselves to engage more effectively in the emerging and developing HTA processes. In the rare disease field specifically, EURORDIS regularly includes HTA in its training programmes for members and, on a broader level, the European Federation of Neurological Associations (EFNA) has initiated a Patient Academy / HTA Course, organised in conjunction with the London School of

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Economics, which, despite the focus of initiating patient representation, has included patient representatives from a large variety of disease areas amongst the participating 'students'.

These views are reinforced from feedback from workshops, including one run in 2010 by EPPOSI, in which it was reiterated that patient participation in HTA is invaluable as patients are able to provide both a unique perspective and real-life experience of the disease. According to the outcomes of the workshop, this means that patients can thus relate to, and expand on evidence of efficacy generated from, for example, clinical trial results, they can contribute to economic models on treatment preferences and the burden of disease, and they can provide invaluable insights into living with the disease and the unmet medical needs that inform value judgements in the HTA process.

> *Not only are they (the patients) the only ones to know the full implications of a disease and its treatment but a greater sense of engagement leads to greater commitment to treatment.*

For additional information, please see *www.epposi.org*, Patient Engagement in Health Technology Assessment (HTA) 2nd Workshop 17 November 2010 Thon Hotel City Centre, Brussels, Belgium.

Recommendations from the workshop were:

1. Every HTA agency should create a clear policy outlining how they will involve patients in the HTA process.
2. Patients must be educated to better understand the concepts underpinning HTA so they understand how to contribute evidence that provides added value to the process.

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3. Increasing patient engagement will take manpower and resources and should be transparent.
4. Collaboration: the only way to achieve real patient engagement in HTA is through greater collaboration between patients, HTA agencies, clinicians, academia and industry and to be clear about where and how collaboration can take place.

Following on from this workshop, together with a series of meetings with patients' organisations, science, industry, HTA agencies and policymakers, EPPOSI's Advanced Innovation Programme in Health Technology Assessment (AIP-HTA) was launched in 2011 with the aim of:

- identifying deficiencies in current HTA policies and structures;
- developing a new framework that can deliver better outcomes for all stakeholders.

These aims were captured in the following question: 'How can HTA agencies at national level better consider societal benefits as an integral element of the HTA core model which positively contributes not only to the realisation of better health outcomes for EU citizens but also contributes to a smart, sustainable economy at EU level?' (*www.epposi.org/index.php/aip-hta/111-stakeholder-survey-on-a-societal-benefits-approach-to-health-technology-assessment)*

As social and ethical considerations are not well defined in the definition of HTA, this is an area where patient organisations such as EURORDIS may be able to make a positive contribution.

Over the course of the next 3 years, the AIP-HTA aims to develop an innovative European framework for a societal benefits approach to HTA with workable templates for implementation at the national level.

So what can patients bring to HTA, given it is an 'evidence-based' process?

Whilst patients will have something to say about all aspects of HTA, the most important contribution they can make is a description of the benefits or unwanted effects of a healthcare technology.

However, it is often not easy to understand how to put these important views, needs and preferences into a form of evidence that can be used by HTA institutions. That is why it is so important for patients to understand HTA and be involved in its definition and assessment.

To that end, and specifically in the field of rare disease, HTA was the focus theme at the EURORDIS Summer School in September 2010. More than 30 patient representatives were introduced to the main HTA assessment tools by academics, public health experts and – crucially – representatives from HTA agencies as well as from industry. In addition, patient representatives had an opportunity to present their HTA experiences in a panel discussion.

It is anticipated that further efforts to improve coordination and harmonise the assessment tools used by the main HTA agencies in Europe will be driven by EUnetHTA, which is a collaborative, cross-Member-State initiative, supported by the EU, to improve coordination and harmonise the assessment tools used by the main HTA agencies in Europe. Rare disease concerns are expressly captured in the work of the EUnetHTA – EURORDIS is one of four patient representatives at the EUnetHTA Stakeholders Forum.

EURORDIS has stated their belief that HTA is 'starting to have and will increasingly have a direct impact on the reorganisation of health services for rare disease patients, including centres of expertise, registries, drugs, standards of diagnosis and care, training for professionals and information' (Le Cam 2010). They have stated their understanding of the

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importance of HTA because of its direct links to patient access and to quality of care.

If used with a purely economic approach, HTA can raise major challenges of patient access to care, but it 'also has the potential to help regulate the offer for care based on quality, relative effectiveness and cost-effectiveness, as well as to redefine consistent patient-centred healthcare pathways for long-term quality and sustainability of healthcare services' (Le Cam 2010).

In order to eliminate the bottleneck of pricing, reimbursement and policy, EUCERD has developed a recommendation to the European Commission (CAVOMP) and the Member States on ways to increase the information available during the development, authorisation and availability of orphan drugs. This is based on collaboration and would encourage early dialogue between all stakeholders from the first stages of orphan drug designation, to facilitate collaboration amongst authorities and Member States in order to make the most of already existing information at the EU level. The objective is to help national health authorities make their pricing and reimbursement decisions based on the best available data, thus improving timely and effective access to the most appropriate treatment by rare disease patients.

This approach has been recommended by consensus by all 27 Member States, industry and patient groups in the framework of the EU Pharmaceutical Forum (*http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm*).

It was further endorsed by the EU Commission's Communication on Rare Diseases (*http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf*) and the EU Council Recommendation on an Action in the Field of Rare Diseases (*http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF*).

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The EUCERD recommendations (see also Chapter 5 – CAVOMP) are that dialogue start at the time of orphan designation between all stakeholders, and continue throughout the drug development. At the time of Marketing Authorisation, a compilation report of all the existing evaluations conducted by the EMA's scientific committees will be made available to the Member States. This information will be supplemented on an ongoing basis by an agreed evidence generation plan, which will gather the in-life outcomes of an orphan drug post-authorisation. The idea is based on European collaboration and the need to address the scarcity of data, due to the rarity of the disease. The outcomes are aimed at facilitating informed decision-making by the Member States by gathering information at a European level, rather than relying on solely national datasets that will, by the very nature of the diseases in question, be limited in patient numbers.

The EUCERD recommendations are intended to serve as a basis for discussion between the principal stakeholders at the European level, including the relevant services of the European Commission, the EMA, HTA bodies, payers, patients and industry. An overview of the proposed process is provided in Figure 7.1.

The final version was published in September 2012. Further information can be downloaded from:

www.eucerd.eu/?p=1699
www.eucerd.eu/?post_type=document&p=1446

MOCA

Pricing and reimbursement has been identified as another area where there are shared challenges between the different Member State governments. MOCA is an initiative from the EU Commission, under the 'Process on Corporate

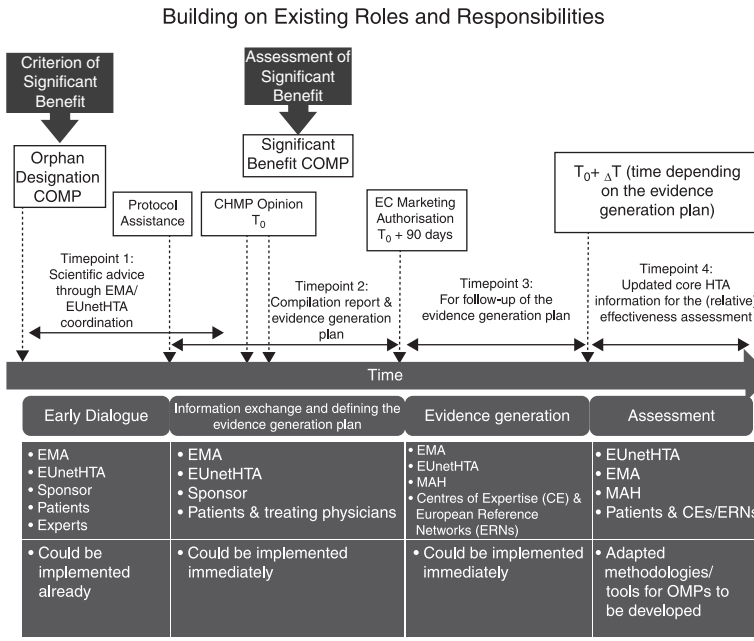

Figure 7.1 **Information flow as recommended by EUCERD**

Source: Reproduced from *www.eucerd.eu/?post_type=document&p=1446*

Responsibility in the field of Pharmaceuticals', established by European Commissioner Tajani. The MOCA project aims to establish concrete deliverables and processes to address the shared access challenges, based on collaboration. It foresees a shared, voluntary, non-legislative, non-regulatory mechanism or approach to address the shared challenges.

The MOCA project was launched in December 2010 under the auspices of the Belgian EU Presidency and is chaired by the Belgian pricing and reimbursement authorities, together with participation from some 10–15 other Member State authorities.

The project seeks to achieve coordination between stakeholders and Member States at EU level to provide 'real access to a real solution (orphan drug) for real patients with

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real Unmet Medical Needs, for which these solutions would otherwise be out of reach – in an affordable and sustainable way' (*http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/tor_orphans_en.pdf*) (-> 'real life access'). The project is running on a voluntary basis, given the fact that pricing and reimbursement remains a national, Member State responsibility. The hope is that it will contribute to developing a process for coordinated access to orphan medicinal products based on the set up of programmes between companies and groups of competent authorities and building as the next step on the outcomes of the ongoing project on a mechanism for CAVOMP information flow, as detailed above.

Further information can be downloaded from: *http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/index_en.htm*

7.7.2 USA

In the USA, NORD is a patient advocacy group formed from a federation of voluntary health organisations, with the aim of helping the nearly 30 million Americans with rare orphan diseases and assisting the organisations that serve them. They do this through programmes of education, advocacy, research and service (for further information, please also see Chapter 3).

As part of their advocacy programme, on 11 January 2012, NORD submitted an *amicus curiae* or 'Friends of the Court' brief in support of upholding the Patient Protection and Affordable Care Act (PPACA), (or 'healthcare reform'), along with 13 other national patient advocacy organisations, including Friends of Cancer Research, the March of Dimes Foundation and others. This Act of 2010 contains an important provision that bars healthcare insurers from

discriminating against people with pre-existing conditions, including many with rare diseases, by refusing them participation in the healthcare coverage marketplace.

One further initiative that patient advocacy organisations have provided input to (including NORD, together with medical experts from the NIH) is the Compassionate Allowances Program, administered by the US Social Security Administration (SSA). This programme was established in 2008 with an initial list of 50 diseases identified by medical experts as ones that routinely meet SSA's criteria for disability benefits. These conditions involve cancers and neurological and other rare diseases affecting adults and children. The programme doesn't guarantee approval for disability benefits but rather provides an expedited review so that individuals with diagnoses on the list receive fast-track review and are notified of the final decision within days rather than months or years.

New Compassionate Allowance Conditions added by the SSA are:

1. Alstrom Syndrome
2. Amegakaryocytic Thrombocytopenia
3. Ataxia Spinocerebellar
4. Ataxia Telangiectasia
5. Batten Disease
6. Bilateral Retinoblastoma
7. Cri du Chat Syndrome
8. Degos Disease
9. Early-Onset Alzheimer's Disease
10. Edwards Syndrome
11. Fibrodysplasia Ossificans Progressiva
12. Fukuyama Congenital Muscular Dystrophy

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13. Glutaric Acidemia Type II
14. Hemophagocytic Lymphohistiocytosis (HLH), Familial Type
15. Hurler Syndrome, Type IH
16. Hunter Syndrome, Type II
17. Idiopathic Pulmonary Fibrosis
18. Junctional Epidermolysis Bullosa, Lethal Type
19. Late Infantile Neuronal Ceroid Lipofuscinoses
20. Leigh's Disease
21. Maple Syrup Urine Disease
22. Merosin Deficient Congenital Muscular Dystrophy
23. Mixed Dementia
24. Mucosal Malignant Melanoma
25. Neonatal Adrenoleukodystrophy
26. Neuronal Ceroid Lipofuscinoses, Infantile Type
27. Niemann-Pick Type C
28. Patau Syndrome
29. Primary Progressive Aphasia
30. Progressive Multifocal Leukoencephalopathy
31. Sanfilippo Syndrome
32. Subacute Sclerosis Panencephalitis
33. Tay Sachs Disease
34. Thanatophoric Dysplasia, Type 1
35. Ullrich Congenital Muscular Dystrophy
36. Walker Warburg Syndrome
37. Wolman Disease
38. Zellweger Syndrome.

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7.8 Compassionate use (expanded access)

Compassionate use is generally understood to cover the provision of unauthorised medicines (i.e. without a marketing authorisation) with assumed benefit to patients with chronic, seriously debilitating or life-threatening disease in situations where alternative treatment options are either non-existent, unsatisfactory or have been exhausted.

There are different mechanisms in Europe and the USA.

7.8.1 Europe

A frequent cause of confusion is that compassionate use in Europe has been used as an umbrella term for a range of country-specific legal provisions, such as 'named patient' or 'nominative' prescriptions, 'temporary use licence', 'humanitarian use' or 'physician's use importation'.

The long-standing legal basis for named patient schemes in the EU is Article 5 (1) of Directive 2001/83/EC on human use medicinal products, which provides sponsors with an exemption to the general requirement for a marketing authorisation before they put the product into the distribution chain or provide it to patients. Article 5 states that a Member State may:

> *. . . in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by his individual patients on his direct personal responsibility.*

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Two cases are discussed below:

- An application for marketing approval has either been or is about to be submitted by the pharmaceutical company developing the drug in the country concerned. Then the company submits a temporary regulatory approval to the administrative authority for a group of patients (Temporary Use Authorisation cohort in France and in Italy, or compassionate use authorisation in the other European countries) that is valid for a limited time span in the country considered.
- Or: The physician asks the administrative authorities for a nominative temporary regulatory approval that is valid for a specific patient and for a limited time span in the considered country.

A summary of 'compassionate use' regulations in ten European countries is given in Table 7.1. It can be seen that although these provisions are not designed for widespread access to orphan drugs, they can offer some hope to a limited number of orphan disease patients.

7.8.2 USA

Patients would usually only have access to unauthorised medicines if on a clinical trial, but one other possible route is through compassionate use, if the pharmaceutical company is willing to provide the drug.

The process, as administered by NORD, is the following:

- The doctor refers the patient in need of a drug to a contract research organisation (CRO), which is an entity that collects scientific data for protocols.
- The CRO collects demands from doctors and sends them to NORD.

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Table 7.1 Summary of 'Compassionate use' regulations in ten European countries (Whitfield et al. 2010)

Country	'Compassionate use'	Responsibility	Competent Authority	Reporting
Austria	Termed 'Named patient use' Treatment of individuals Separate from clinical trial	Treating physician	N/A	No
Denmark	Termed 'Compassionate use permit' Treatment of individuals Consent to disclose health data required	Treating physician	Danish Health and Medicines Authority *http://laegemiddelstyrelsen.dk/en/*	Adverse events reported to the national Competent Authority
France	Termed 'Temporary authorisation for use' for individuals, or 'Cohort temporary authorisation for use' Separate from clinical trials	For 'nominative' use the prescribing physician, for 'cohort' use the licence holder	National Agency for the Safety of Medicine and Health Products *www.ansm.sante.fr/*	All adverse reactions. Periodic report for 'temporary authorisation for use' programmes
Germany	National legislation and guidelines Informed consent required	'Responsible person'	Federal Institute for Drugs and Medical Devices *www.bfarm.de/*	Serious adverse events reported to authorising agency within 15 days
Hungary	No specific legislation	N/A	National Institute of Pharmacy *www.ogyi.hu/*	N/A

Ireland	The product must be between a phase III trial and marketing authorisation Guidelines	Prescribing physician	Irish Medicines Board *www.imb.ie/*	No
Italy	Termed 'Compassionate use' for individuals Informed consent required	Treating physician	Italian Medicines Agency *www.agenziafarmaco.it/*	No
Spain	Termed 'Compassionate use' for individuals Informed consent required Separate from clinical trials	Treating physician	Spanish Agency for Medicines and Health Products *www.agemed.es/*	Efficacy and adverse events reported to the national Competent Authority
Sweden	Guidelines	N/A	Medical Products Agency *www.lakemedelsverket.se/*	N/A
UK	Termed 'compassionate use' or 'expanded access' using 'specials' for individual patients Guidelines	Prescribing physician	Medicines and Healthcare Products Regulatory Agency *www.mhra.gov.uk/*	Serious adverse reactions reported to the national Competent Authority

- NORD checks that each demand is complete (e.g. it must include a patient consent form, the patients must comply with other rules of the protocol, and they must qualify under strict medical criteria).
- NORD then enters the demands in a database and performs a 'computerised random selection' to select the patients who will benefit from the programme.
- NORD notifies non-selected and selected patients, as well as their doctors and the pharmaceutical company.

These programmes are sometimes referred to as lotteries, because the selection process is totally random and the frequency and number of patients selected are determined by the pharmaceutical company. The percentage selected varies according to the amount of the drug given by the company and the number of demands, but patient advocacy groups, including NORD, are sitting down with rare disease organisations and pharmaceutical companies to see whether guidelines can be developed to make this process more transparent.

One further route for patient access is under a treatment Investigational New Drug (IND). The following summary is taken from the FDA website:

> *Treatment Investigational New Drugs. . . are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished.*

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> *. . . Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies.*
>
> (*www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/PatientInvolvement/ucm123872.htm*)

7.9 Note

1. *http://www.eurordis.org/content/survey-patients%E2%80%99-access-orphan-drugs-europe*

7.10 References

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