

BENCHMARKING SUCCESS

Evaluating the Orphan Regulation and its impact on patients and rare disease R&D in the European Union

This report was initiated and funded by Shire International GmbH. Shire is now part of Takeda. The views represented here are those of the authors only.

Copyright © Pugatch Consilium 2019

The moral right of the authors has been asserted.

All rights reserved. Without limiting the rights under copyright reserved above, no part of this publication may be reproduced, stored or introduced into a retrieval system, or transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise), without the prior written permission of both the copyright owner and the publisher.

CONTENTS

LIST OF ABBREVIATIONS	5
EXECUTIVE SUMMARY	7
INTRODUCTION AND ISSUE OVERVIEW	15
1 THE CHALLENGES IN DEVELOPING A BIOPHARMACEUTICAL TREATMENT FOR RARE DISEASES	17
1.1 The biopharmaceutical R&D process	17
1.2 Developing new treatments for rare diseases – a critical challenge	18
2 OVERCOMING THE CHALLENGES: ORPHAN LEGISLATION IN THE EU AND GLOBALLY	21
2.1 The EU Orphan Regulation – An overview	21
2.2 The patchy status of orphan medicinal product development schemes worldwide	24
3 THE IMPACT OF THE EU ORPHAN REGULATION ON ORPHAN DESIGNATIONS AND ORPHAN PRODUCT APPROVALS	25
4 THE IMPACT OF THE EU ORPHAN REGULATION ON CLINICAL RESEARCH ACTIVITY INTO RARE DISEASES	31
5 MORE RESEARCH, MORE DESIGNATIONS, MORE PRODUCTS, BUT WHAT ABOUT ON-THE-GROUND PATIENT ACCESS?	39
CONCLUSION	45
NOTES	46

CONTENTS (continued)

TABLES AND FIGURES

Figure 1	The biopharmaceutical R&D process	18
Table 1	Unique challenges in developing a treatment for rare diseases	19
Table 2	Criteria for achieving an orphan designation under the EU Orphan Regulation	21
Figure 2	Incentives for orphan medicinal product development under the EU Orphan Regulation	22
Table 3	Developing an orphan medicine: A critical global challenge without enough support and incentives	24
Figure 3	Annual rates of applications for orphan designation and approval and COMP opinions, 2000-2017	25
Figure 4	Annual rate of approval of orphan medicinal products by the EMA and the FDA, 2000-2017	26
Figure 5	Annual rate of approval of orphan medicinal products that also treat paediatric populations v. adult populations only, 2000-2017	27
Figure 6	New clinical trials on rare diseases, selected economies / region, 2006-2016	32
Figure 7	New clinical trials on rare diseases in the EU-5 countries, 2006 v. 2016	33
Figure 8	Enrolment rate for clinical trials on rare diseases in the EU-5 countries, 2006-2016	34
Figure 9	Enrolment rate for clinical trials on rare diseases in the EU-5 countries, 2006 v. 2016	34
Figure 10	New early-phase clinical trials on rare diseases, selected economies / region, 2006-2016	35
Figure 11	New clinical trials on rare diseases using biologic medicines, selected economies / region, 2006-2016	36
Figure 12	Access to orphan medicinal products in the EU-5 countries: Rates of and time to reimbursement	40
Figure 13	EURORDIS Access Campaign: Rates of patients with rare diseases reporting insufficient reimbursement as an obstacle to receiving proper treatment, 19 European countries, 2016	41
Figure 14	EURORDIS Rare Barometer survey: Differences in access to treatment between patients with rare diseases and the general population	42

LIST OF ABBREVIATIONS

CAGR	Compounded Annual Growth Rate
COMP	Committee for Orphan medicinal Products
EC	European Commission
EMA	European Medicines Agency
ERN	European Reference Networks
EU	European Union
EURORDIS	European Organisation for Rare Diseases
FDA	United States' Food & Drug Administration
HTA	Health Technology Assessment
IP	Intellectual Property
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
OHE	Office of Health Economics
P&R	Pricing & Reimbursement
R&D	Research & Development
RCT	Randomised Clinical Trial
SME	Small & Medium Enterprise
SPC	Supplementary Protection Certificate
UK	United Kingdom
US	United States of America
USD	United States Dollars



EXECUTIVE SUMMARY

Developing a novel biopharmaceutical product is an expensive, risky and time-consuming enterprise that takes between 10 to 15 years on average at an estimated total cost of USD2-2.6 billion.

Developing a novel biopharmaceutical product that targets a rare disease (called orphan medicine) is an even more challenging process; patient populations are significantly smaller and less is known about individual diseases.

Acknowledging the challenges in orphan medicinal product development, many countries have enacted laws and developed special programs to encourage orphan medicinal product development through regulatory and financial incentives such as tax credits, research grants, a faster and cheaper market approval process and scientific assistance, and, most importantly, a defined period of market exclusivity. This includes the European Union which in 1999 introduced Regulation (EC) No 141/2000 (the "Orphan Regulation").

In light of the EU Commission's current consultation on paediatric medicines and rare diseases – *Evaluation of the legislation on medicines for children and rare diseases (medicines for special populations)* - the purpose of this report is twofold.

First, to assess whether the EU Orphan Regulation has accomplished its aim of incentivising R&D into rare diseases and the development and

introduction of new products and therapies onto the EU market. How, for example, has the Orphan Regulation affected rates of product development and clinical research in the EU? Are there more products and therapies for rare diseases approved and on the market in the EU today than in 1999? Similarly, are there more or fewer clinical trials taking place today in the EU than prior to 1999 and the passage of the Orphan Regulation?

Second, the report seeks to examine some of the current and future big challenges and questions about R&D and new product development for rare diseases. This includes questions such as how to continue to incentivise the development of orphan drugs specific for paediatric use? How to ensure real patient access to new medicines after product registration and market authorisation is complete? And how to continue to provide effective incentives through defined market exclusivity periods?

One key feature of the report is that it draws upon the expertise and insights and ideas from a panel of leading experts drawn from the medical, regulatory and academic field. Their thoughts and insights are interwoven throughout the report.

Key findings

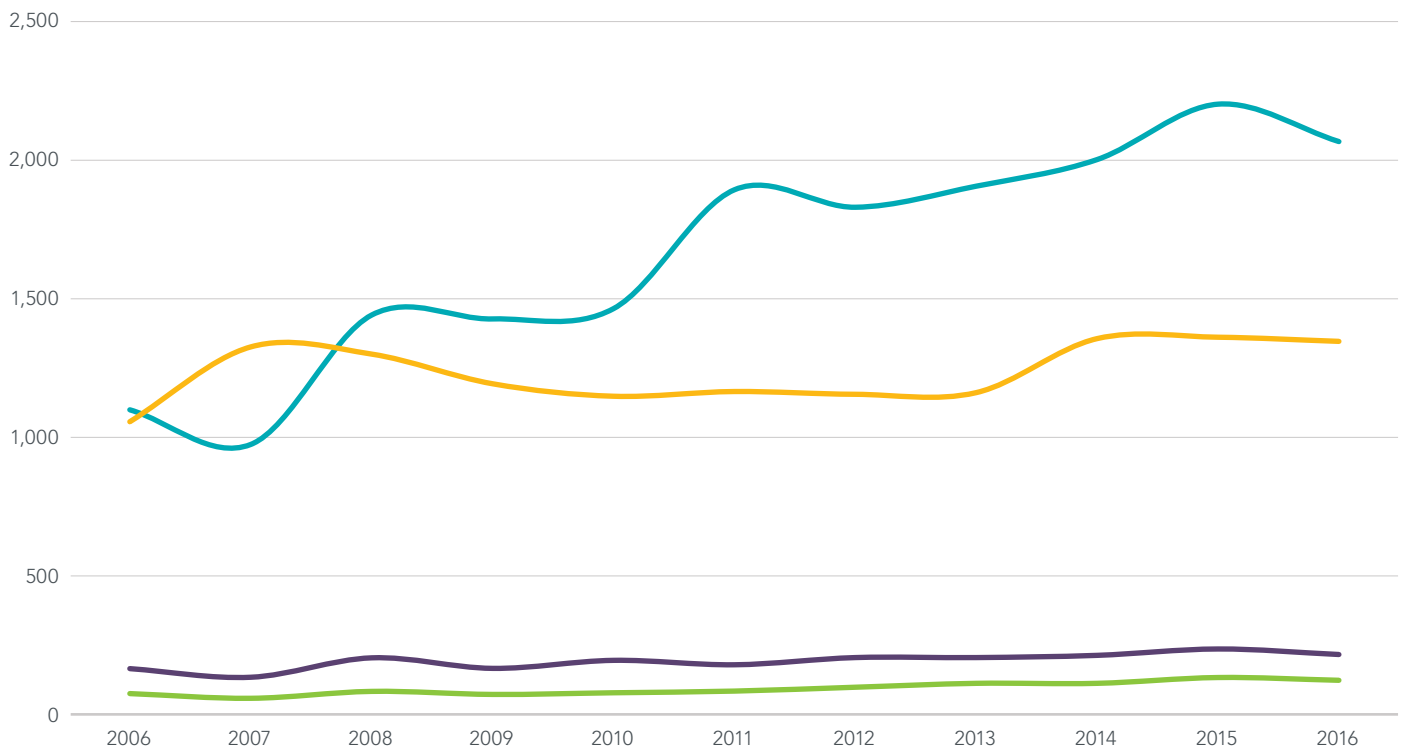
In its first evaluation of the EU Orphan Regulation accomplishments in 2006 the EC concludes that “the orphan legislation in the EU has far exceeded initial expectations”.¹ 12 years on, looking at the number of approved orphan medicines and levels of clinical research into rare diseases, the EU Orphan Regulation can unequivocally be viewed as a success.

Key finding 1: Clinical research on rare diseases has surged in the EU over the last decade

- The EU region has seen **the strongest growth** in clinical research on rare diseases since the mid-2000s globally: Annual activity has increased by 88% between 2006 and 2016, with the EU-5 countries experiencing an even bigger increase of 104% during that period.

- The EU-5 countries are also regional leaders in providing rare diseases patients with early access to potential treatment through clinical trials: some 2.37 million patients were enrolled to clinical trials on rare diseases in the EU-5 countries alone between 2006 and 2016.
- During that period, Canada and Australia, which otherwise experience high levels of clinical trial activity yet offer no special incentives for orphan medicinal product development witnessed a decade-long stagnation in very low levels of clinical trial activity on rare diseases.

New clinical trials on rare diseases, selected economies / region, 2006-2016

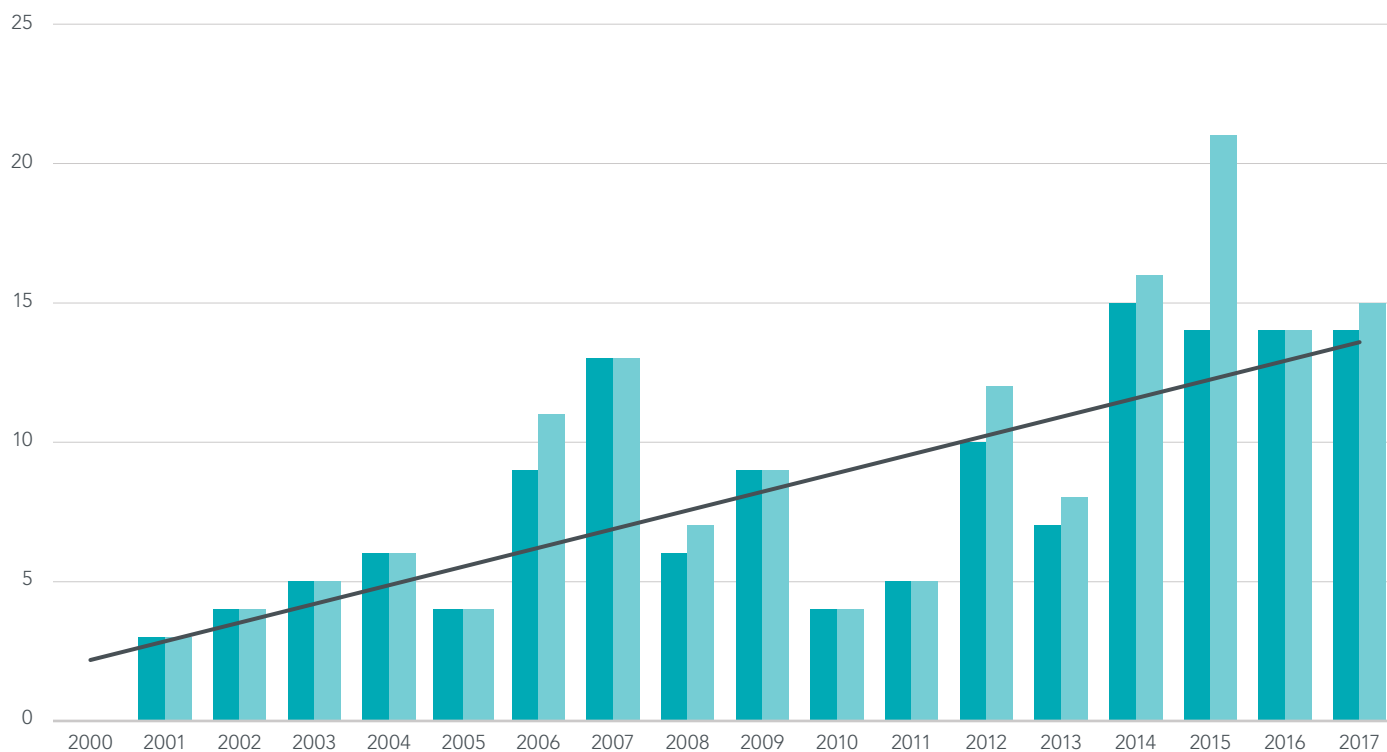


Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

Key finding 2: Since the introduction of the EU Orphan Regulation the number of orphan designations and orphan medicinal product approvals have increased annually.

- In the past 17 years of its existence, the EU Orphan Regulation has resulted in:
 - Nearly 2,000 orphan designations approved (60% of which target rare diseases with a prevalence below 1 in 10,000, with most lacking any previously approved treatment in the EU), growing at a CAGR of 14.8%;
 - Over 150 orphan medicinal products approved by the EMA for over 90 rare diseases (up from only 8 orphan products available in 2000), growing at a CAGR of 10.8% – with more than a third of these also treating paediatric populations;
 - An increase of 85% in the number of rare diseases for which an orphan designation exists in the EU (more than 80% of these rare diseases affecting paediatric populations).
 - Significant growth in the number of SMEs, which are responsible for 72% of orphan designations and medicinal products.

Annual rate of approval of orphan medicinal products by the EMA, 2000-2017



■ Orphan medicinal products authorised ■ Orphan designations included in authorised therapeutic indication

Source: Committee for Orphan Medicinal Products (COMP), meeting report on the review of applications for orphan designation, September 2018, Annex I; analysis: Pugatch Consilium

Key finding 3: Despite the success of the Orphan Regulation in placing more orphan medicines on the EU market, substantial discrepancies exist in access to these medicines between Member States

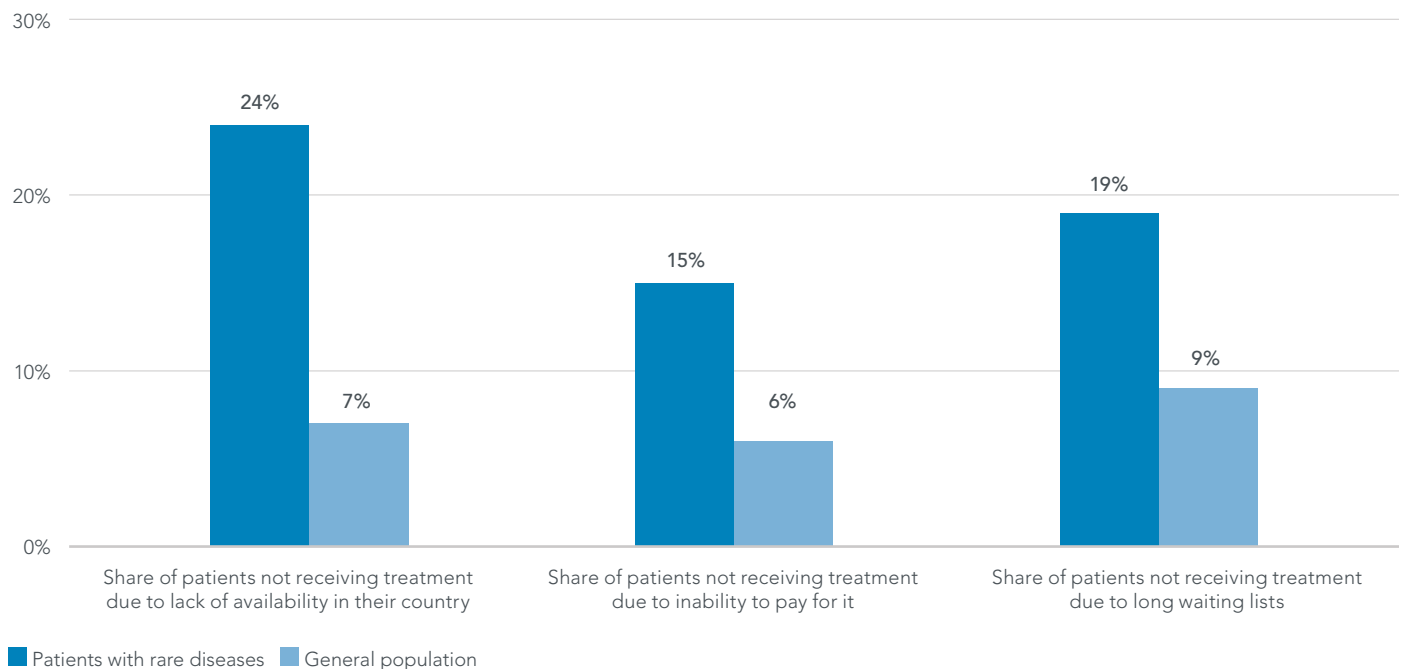
- Timely and equitable access to orphan medicines is not guaranteed in the EU:
 - Members States vary greatly in both the number of products publicly reimbursed and the average time it takes for patients to gain access to them: Discrepancies can surpass 50% in the number of publicly-reimbursed products and over 24 months in time to reimbursement decisions between Member States.

- Insufficient reimbursement is cited as a major obstacle in access to treatment by more than 20% of patients with rare diseases in 10 out of 19 sampled European countries in EURORDIS' Rare Barometer survey.

- The share of patients in the EU with rare diseases reporting lack of access due to insufficient reimbursement, lack of affordability or long delays is between two to three times higher compared to the general population!

- These findings suggest that the health and societal value of innovative orphan medicines is perceived differently, and is not acknowledged by all Member States.

EURORDIS Rare Barometer survey: Differences in access to treatment between patients with rare diseases and the general population



Source: EURORDIS Access to treatment: unequal care for European rare disease patients - A Rare Barometer survey, February 2017; No. of respondents: 1,350, from 21 European countries; analysis: Pugatch Consilium

Looking towards the future: Concluding thoughts

Building on the insights provided by the pool of experts interviewed as part of this project, this report offers potential solutions on how to face some of the current and future big challenges and questions about R&D, new product development and patient access for rare diseases. This includes, for example, complementary initiatives, utilized through collaborative efforts and commitment, that could address the discrepancies found in market access and deliver better healthcare for EU patients with rare diseases. Below are three potential solutions to some of these major policy challenges.

1. Improving value assessment and reducing delays by harmonising the clinical aspects of the HTA process

Given the considerable differences in the duration of the reimbursement decision process between EU Member States, efforts could be directed towards the harmonisation of the clinical aspects of the HTA processes for orphan medicinal products across EU Member States. Indeed, a proposal for a Regulation on HTA has been

published earlier this year by the EC, opting for early dialogue and a legislative framework for joint assessment of the clinical aspects of the HTA. The EC estimates that this initiative would have a significant social and economic impact realised through reduced duplicative efforts and cost savings, expedited market access to innovative products (by 2 to 6 weeks) as well as an improved decision-making process and predictable regulatory process with regards to generation of clinical evidence. This presents a unique opportunity for promoting healthcare system sustainability and better public health throughout the EU.

However, in order to create an effective framework for collaboration that would eliminate the delays caused by duplicative efforts and differences in technical capacity at a national HTA level, while retaining Member States' mandate in performing their own assessments for guiding pricing and reimbursement decisions, the joint HTA process should be mandatory and limited to the clinical aspects alone, while providing the opportunity for early dialogue on clinical data requirements and comparator selection for the regulatory approval and joint assessment, through a joint scientific consultation.



Johan Van Calster

Managing Director, CLIVAN bvba, Policy and Governmental Affairs Office for Medicinal Products; former Management Board Member of the EMA and former Director General at the Directorate-General for Medicinal Products, the Federal Public Service for Public Health, Food Chain Security and Environment, Belgium.

Equitable access to treatment for patients with rare diseases is the third pillar of the EU Orphan Regulation. The gaps in access to treatments between EU-Member States – particularly vis-à-vis the relative success of the Orphan Regulation in driving research and development of orphan medicines – should capture the focus of improvement efforts. The orphan designation and marketing authorisation of orphan medicines

are only the first steps; these treatments must be accessible by EU patients following a uniform Health Technology Assessment (HTA), conducted under clear guidelines and principles of social responsibility, and whose outcomes are preferably accepted by all the Member States.

2. Creating dedicated pathways that are based on early multi-stakeholder dialogue and real-world evidence

Generating sufficient clinical evidence for the approval of an orphan medicinal product is extremely challenging, given the scarcity and geographical dispersion of patients. A framework that enables early dialogue between the developers of orphan medicinal products that show promise early in the development stage and regulators within EMA could facilitate earlier access to innovative treatments, while ‘real-world usage data’ supplements the body of evidence generated in the clinical trials stage. The utilisation of early dialogue and the generation of real-world evidence would reduce uncertainties with regards to the evaluated product’s safety and efficacy profile, leading to more informed and effective decision-making processes, both at the EU level and at the Member States’ level. The

framework for such a process already exists at the EU level within the EMA as ‘adaptive pathways’ and the Innovative Medicines Initiative’s ADAPT-SMART project. At a Member State level, multi-stakeholder initiatives such as TRUST4RD – a Tool for Reducing Uncertainties in the evidence generation for Specialised Treatments for Rare Diseases – facilitate a shared understanding of the challenges faced by manufacturers, regulators, HTA bodies, payers and patient groups in the development and use of real-world evidence to address uncertainties for rare disease treatments.²

Creating dedicated pathways based on existing principles and methodologies, while acknowledging the unique challenges in developing an orphan product (including the substantial costs of generating real-world evidence), could both increase the number of approved orphan products as well as shorten their time-to-market.



Johan Van Calster

Managing Director, CLIVAN bvba, Policy and Governmental Affairs Office for Medicinal Products; former Management Board Member of the EMA and former Director General at the Directorate-General for Medicinal Products, the Federal Public Service for Public Health, Food Chain Security and Environment, Belgium.

The ‘adaptive pathways’ programme by the EMA has facilitated the gradual build-up of clinical evidence while enabling early access to innovative products. That is a very good approach. Yet it must go hand-in-hand with the utilisation of real-world evidence through existing and improved

cross-border framework and early dialogue between the developers and the regulators, in order to reduce uncertainties and reach an informed decision-making process that will be highly beneficial for all stakeholders, most importantly for the patients.

3. Enhancing R&D productivity by utilising the potential of advanced technologies and increasing Member States' involvement, for example through the European Reference Networks (ERNs)

The field of clinical research does not remain unresponsive to technological advancements. Big Data mining, bioinformatics and Digital Health platforms are already changing the healthcare landscape, and hold tremendous potential to increase R&D productivity. Efforts should also be directed towards the harmonisation of clinical trial design, execution and data sharing. These would enable the establishment of the safety and efficacy profiles of potential treatments early in the development process, thus increasing productivity as well as shortening the time to market for promising orphan products.

Yet the effective utilisation of the advanced research infrastructure for the benefit of all EU patients with rare diseases also requires the commitment and active participation of EU Member States in supporting EU-wide research coordination efforts through the European Reference Networks (ERNs) – which encompasses over 300 hospitals and 900 specialised teams, and utilises various instruments with the purpose of ensuring proper access to specialised healthcare across the EU – as well as by creating national databanks and patient registries to facilitate outreach and recruitment, and encourage more local R&D activity – particularly clinical research – by offering incentives at a national level, such as tax reductions for clinical trials, fee waivers, and streamlined regulatory processes for clinical research.



Robert Madelin

Chairman & Partner, Foresight International Policy and Regulatory Advisers (FIPRA) International; former Senior Adviser for Innovation, Director General for Communications Networks, Content and Technology (CONNECT) and Director General for Health and Consumer Policy (SANCO) at the European Commission.

We now have the enabling infrastructure for cross-border collaboration and pan-European data sharing, for example through the European Reference Networks, yet we are still behind the

curve in utilising our abilities to promote cutting-edge research even further, to the benefit of all stakeholders involved, most importantly the patients.



Bernard Merkel, PhD

Special Advisor for healthcare issues, Foresight International Policy and Regulatory Advisers (FIPRA), Belgium; former Head of Health Strategy at the European Commission.

The EU Orphan Regulation has played a key role in promoting the conceptualisation of rare diseases as a European issue par excellence. Conjointly with a series of initiatives at both the pan-European and Member State levels, the EU Orphan Regulation demonstrated the genuinely important role that the European Commission has played in promoting public health in the field of rare diseases for the entire European Union. This thinking drove later initiatives such as the Cross-Border Healthcare Directive, and

the establishment of the European Reference Networks. In addition to the health and social benefits there was the expectation that the incentives would support the development of the European research-based industry. In my view, the thinking behind the EU Orphan Regulation and additional initiatives made in the field of rare diseases in the EU constitute an excellent example of the solidarity and cohesiveness that constitute a major added value of the EU Orphan Regulation.



INTRODUCTION AND ISSUE OVERVIEW

“It is not unusual to have a rare disease.”
EURORDIS³

What is a rare disease?

- Rare diseases comprise a wide range of complex conditions that are associated with chronic, progressive, degenerative and/or life-threatening symptoms that affect a relatively small portion of the population.
 - The definition of ‘rare’ varies between countries and regions:
 - In the EU a disease is rare if it affects up to 5 of 10,000 people;⁴
 - In the US a disease is rare if it affects less than 200,000 US persons;⁵
 - In Japan the threshold is set at 50,000, but was widened in 2015 to also include ‘intractable diseases’⁶ affecting up to 180,000 Japanese persons.
- About 80% of all rare diseases are of genetic origin.⁷ This means that the disease is present throughout a person’s life, while symptoms may appear at any given time.
- Today there are between 6,000 and 8,000 rare diseases,⁸ with around 250 new conditions described in the medical literature every year⁹ and a growing quantity of disease genes identified.¹⁰

How many patients suffer from rare diseases?

- While individually a rare disease affects only a fraction of the population, the total number of people suffering from rare diseases around the world is estimated at 350 million.
- Rare disease patients are estimated to comprise between 6% to 8% of the EU population – or between 30 to 40 million people.¹¹ Similar figures are estimated for the US.¹²

- Between 50% to 75% of rare diseases affect children.¹³

How do rare diseases impact patients’ lives?

- Rare diseases are responsible for 35% of deaths in the first year of life, with a 30% mortality rate by the age of five.¹⁴
- 80% of patients with rare diseases experience difficulties in completing daily household tasks.¹⁵
- 70% of patients with rare diseases and their carers have reduced or completely stopped their professional activities due to the illness.¹⁶
- Depression is prevalent in 3 times more patients with rare diseases compared to patients with less rare conditions.¹⁷

The value of new products and innovative medicines

- At least 95% of rare diseases do not have any approved medicinal treatment.¹⁸ For many patients with rare diseases, innovative medicines are often the first treatment made available to their condition, and have a considerable positive impact on longevity and quality of life, with notable examples including:
 - The introduction of C1 inhibitors for Heredity Angioedema which lacked any treatment until a decade ago, Elosulfase alfa which provided a first treatment for Morquio A Syndrome, and tetrabenazine which offered a first treatment for Huntington’s Disease,¹⁹ as well as the recently approved eteplirsen injection – a first treatment for Duchenne Muscular Dystrophy,²⁰ and nusinersen – a first treatment for Spinal Muscular Atrophy.²¹

- Biopharmaceutical innovation is also discovering new therapies that offer more effective treatments, as well as improving existing therapies, with notable examples including:
 - The introduction of tyrosine kinase inhibitors (TKIs) for the treatment of Chronic Myelogenous Leukaemia (CML) which tripled the 5-year survival rate, and targeted therapies for Cystic Fibrosis which increased longevity by over 20 years since 2005, and substantially improved CF patients' quality of life.²²
- By reducing disability and hospitalisation days and enabling patients to perform daily functions and work, biopharmaceutical innovation (general and that specific to rare diseases) reduces the economic burden of the diseases on the healthcare system, from the patients and their carers, creating substantial and quantifiable socio-economic value.²³



What else has been done to address this field?

- The body of scientific and medical knowledge has grown significantly: Advanced technologies enable better identification and understanding of the genetic sources and natural history of rare diseases.
- More medicines that treat rare diseases are added to the market each year for more rare conditions, and more clinical research is conducted around the world on thousands of potential novel treatments.
- Hundreds of patient organisations and related associations have been established, making sure that patients' voices are heard and promoting actions for better healthcare for their patients.
- International collaboration between patient organisations, healthcare professionals, regulators, payers and industry has resulted in numerous positive developments, including the communication of knowledge and best practices through international research networks, the establishment of centres of expertise, patient registries and databanks, help lines and many more.

What are the remaining challenges?

- Despite the progress seen over the last few decades, scientific and medical knowledge on the majority of known rare diseases is lacking, and more rare conditions are discovered every year.²⁴
- Ensuring equal healthcare for patients with rare diseases requires securing timely and equitable access to innovative treatments.²⁵
- Studies reveal that over the past decade patients with rare diseases in the EU experience significant gaps and delays in access to their needed treatments. In some rare conditions the lack of timely access may result in irreversible harm to these patients.²⁶

1 THE CHALLENGES IN DEVELOPING A BIOPHARMACEUTICAL TREATMENT FOR RARE DISEASES

Development of new medicines is essential for meeting increasingly greater demand, yet is not an easy endeavor. Developing new medicines for rare diseases is considerably more challenging.

1.1 The biopharmaceutical R&D process

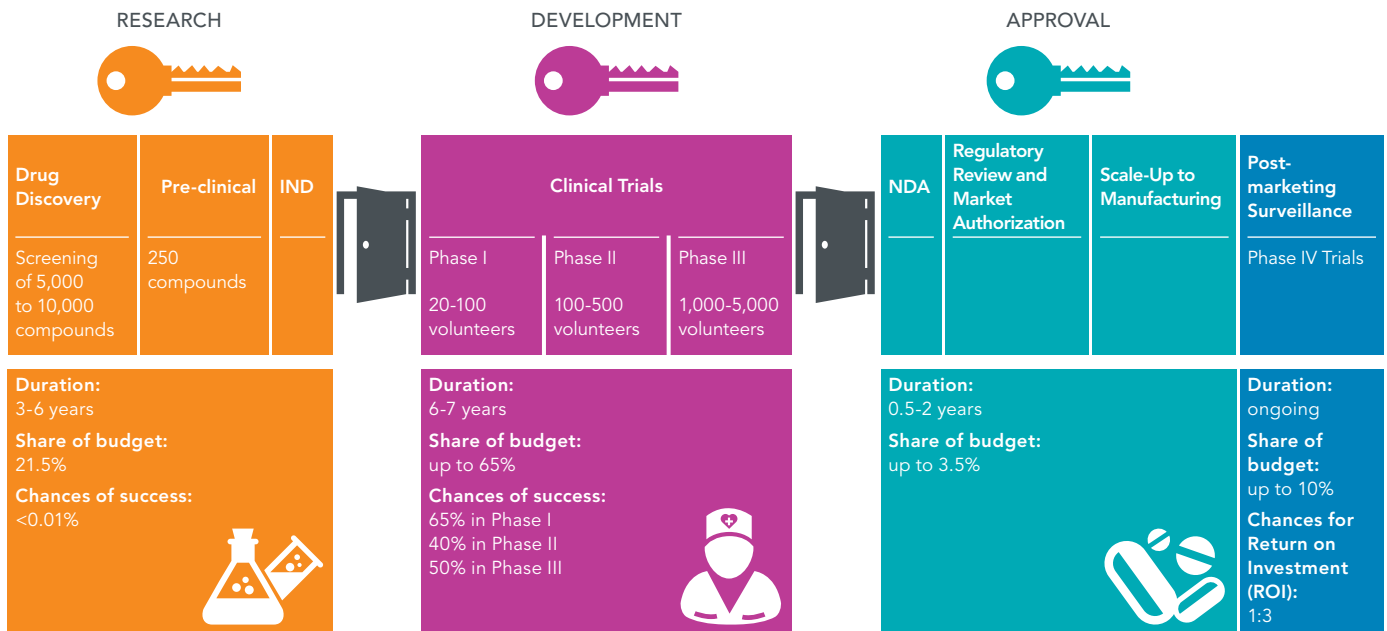
Developing new biopharmaceutical products and treatments is an expensive, risky and time-consuming enterprise:

- Innovative medicine development takes between 10 to 15 years on average, with only 1-2 of every 10,000 potential compounds in basic research successfully becoming a marketable product.²⁷
- The total cost of development is estimated today at USD2-2.6 billion – more than double than the cost of development in 2003.²⁸
- Clinical research is the cornerstone of the drug development process: It provides proof of the safety, quality and efficacy of new medicines or new uses, forms or dosages of existing medicines. It is also the longest and most challenging process where chances of success are only 40%.²⁹
- Over the years the complexity of clinical research has increased significantly, including for example in the number of clinical procedures per trial and eligibility criteria for participation, in the trial duration, staff needed, and reduced patient enrolment and retention rates.³⁰
- Similarly, the complexity and costs of post-marketing surveillance and phase IV trials studies have also increased substantially; in many therapeutic areas the cost of a phase IV trial exceed the costs of other phases in the clinical trial process.³¹
- Yet even following successful approval, the chances for recouping R&D investments are extremely low, estimated at 3.2%.³²

Figure 1 below provides a basic overview of the biopharmaceutical R&D process, with a particular focus on the stages of clinical development:



FIGURE 1 The biopharmaceutical R&D process



Source: Pugatch Consilium; adapted from PhRMA³³ and Nature³⁴

1.2 Developing new treatments for rare diseases – a critical challenge

While the biopharmaceutical R&D process is in itself long, expensive and involves a great deal of risk, developing new innovative treatments for rare diseases is considerably more challenging.

Due to these unique challenges, the process of developing a treatment for a rare disease is longer and riskier than for non-rare diseases:

- A recent study by the Tufts Center for the Study of Drug Development finds that orphan medicinal product development takes 15.1 years (from the first patent filing to product launch) – 2.3 years, or 18% longer than for novel medicines treating non-rare diseases, while the R&D process for ultra-orphan diseases (diseases with a prevalence of less than 1 in 50,000 people) takes even longer - 17.2 years on average.³⁵

- The study (which examined 46 first-in-class orphan novel medicinal products approved by the FDA between 1999 and 2012) reveals that all of the manufacturers responsible for these products have faced at least two of the above-cited challenges, with the majority experiencing four or more.³⁶

Looking to overcome the above cited challenges, developers of orphan treatments are sponsoring the creation and maintenance of hundreds of patient registries across the world, in collaboration with medical organisations and patient groups.³⁷ Though the costs of establishing patient registries and their on-going maintenance are substantial, these patient registries are highly valuable:

- These registries assist in identifying patients from around the world, accelerating recruitment and increase retention rates;

TABLE 1 Unique challenges in developing a treatment for rare diseases

Disease-specific challenges	<ul style="list-style-type: none"> • Rare diseases tend to exhibit high levels of variability in expression, severity, and/or course of the disease – between patients and between sub-groups (e.g. men v. women / child v. adult) • In many cases the natural history and biological mechanisms of the disease are not known or understood • These often lead to incorrect or late diagnosis: A survey of 6,000 patients with 8 rare diseases reveals that 40% of patients first received an incorrect diagnosis, the rest received none
Population-specific challenges	<ul style="list-style-type: none"> • Rare diseases affect very small numbers of population, with high variance in prevalence and geographical distribution • Approximately 50% of patients with rare diseases are children • Thus, rare disease patients’ research recruitment, retention and management can present more challenges
Resources challenges	<ul style="list-style-type: none"> • Conducting a clinical trial requires: <ul style="list-style-type: none"> – identifying researchers and physicians with knowledge and expertise in these highly-specific clinical fields – locating appropriate study sites that have the therapeutic and operational capabilities to conduct a clinical trial and are accessible to selected patients
Commercial challenges	<ul style="list-style-type: none"> • Finally, following regulatory approval, the very limited market size seldom enables research-based manufacturers to cover the costs of research and development

Sources: EURORDIS, EurordisCare2 survey; Murphy, M. F. (2016). “Rare Diseases: Meeting the Unique Challenges of Orphan Drug Development”, Applied Clinical Trials; Tambuyzer, E. (2010). “Rare diseases, orphan drugs and their regulation: questions and misconceptions”, Nature Reviews Drug Discovery, Opinion, AOP; Tufts Center for the Study of Drug Development (2018). Patent-to-launch time for orphan drugs is 2.3 years longer vs. other drugs, Impact Report, Vol. 20, No. 3, May/June 2018; Vickers, J. P. (2013), “Challenges and Opportunities in The Treatment of Rare Diseases”, Drug Discovery World, Spring 2013; analysis: Pugatch Consilium

- Registries also aid in identifying locations for clinical trials and in validating primary and secondary clinical endpoints;
- Registries serve as an essential resource for effective pharmacovigilance through post-marketing surveillance, phase IV trials and gathering real-world evidence;
- Perhaps most importantly, registries also provide a route of communication between patients, medical experts and researchers, where patients’ voices can be heard and used to improve future treatments.³⁸

Summing up

- Developing a new biopharmaceutical treatment is a highly challenging undertaking due to the very long and very risky process whose costs are estimated at over USD2 billion and chances of returning this investment are minuscule.
- These challenges are enhanced significantly when developing a treatment for a rare disease.
- Registries of patients with rare diseases are created and maintained under the sponsorship of biopharmaceutical companies, providing a highly-valuable resource for promoting research and improving patients’ lives.



2

OVERCOMING THE CHALLENGES: ORPHAN LEGISLATION IN THE EU AND GLOBALLY

Acknowledging the challenges in developing new medicines for rare diseases, many countries developed legislation and special programs to encourage development of orphan medicines. This includes the EU which in 1999 introduced Regulation (EC) No 141/2000 (the “EU Orphan Regulation”).

2.1 The EU Orphan Regulation – An overview

Entering into force in January 2000 the purpose of the EU Orphan Regulation was to “lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products”.³⁹

1. The procedure for orphan designation

An orphan designation is a status assigned to a medicinal product that is intended for treating a rare disease.⁴⁰ To achieve an orphan designation, the orphan medicinal product candidate must meet the following criteria:

The Orphan Regulation also establishes that:

- All developers of an orphan medicinal product have to submit a yearly report on the status of development of the designated product.
- All orphan medicinal products must be approved for marketing in the EU by the European Medicines Agency (EMA) alone, through the so-called Centralised Procedure.
- Orphan medicinal product designation is not exclusive, but can be granted to more than one sponsor applying for the same product indicated for the same rare disease.
- Orphan medicines that are approved for marketing in the EU for non-rare conditions (or indications) can extend their indication for treating rare conditions; in these cases the medicine must establish its safe and effective use in patients with the rare condition via clinical trials, and undergo the regulatory approval process.

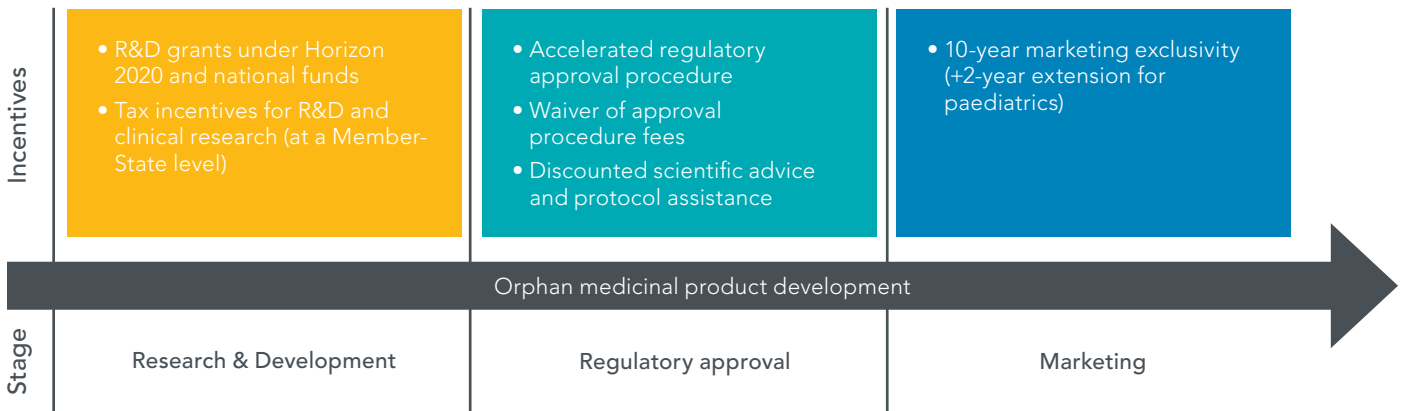
TABLE 2 Criteria for achieving an orphan designation under the EU Orphan Regulation

The ‘prevalence’ criteria	The ‘significant clinical benefit’ criteria
<ul style="list-style-type: none"> • The product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU Community <p>or,</p> <ul style="list-style-type: none"> • That it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment 	<ul style="list-style-type: none"> • That there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the EU <p>or,</p> <ul style="list-style-type: none"> • If such method exists, that the medicinal product will be of significant benefit to those affected by that condition

2. Special incentives for orphan medicinal product development

The EU Orphan Regulation provides a set of incentives for encouraging the development of orphan medicinal products:

FIGURE 2 Incentives for orphan medicinal product development under the EU Orphan Regulation



The incentives offered under the EU Orphan Regulation aim at mitigating the challenges across all the phases of orphan medicine development, from defraying some of the costs and regulatory fees to providing market exclusivity that ensures that orphan medicinal products' developers will have a sufficient timeframe for recouping the high costs of development.

Yet while some EU Member States offer incentives to promote R&D (including reduced fees for national registration, reduced fees for clinical trials and research grants), only two EU Member States have tax credits in place, with a relatively limited scope.⁴¹

Of the incentives offered in the EU, market exclusivity for orphan medicines is usually regarded as the most consequential as it aims to achieve two goals:

1. Ensuring continued innovation in the field of rare diseases by offering research-based manufacturers of orphan products the opportunity to recoup their investments (which would not have been possible otherwise);
2. Creating a sustainable balance between rewarding innovation and containing healthcare spending by encouraging competition immediately upon the expiry of the market exclusivity.

There are, however, several limitations that apply to this incentive:

- First, the orphan product's status can be withdrawn after 6 years if designation criteria are no longer met, including if the product is sufficiently profitable.⁴²

- Second, a similar orphan medicinal product may be granted a marketing authorisation while the orphan market exclusivity is still in force, where:
 - a) a new orphan product targeting the same therapeutic indication is proven to be safer, more effective or otherwise clinically superior;⁴³ or
 - b) the manufacturer is unable to ensure a sufficient supply of the product.⁴⁴
- The development of the European Reference Networks (ERNs) under the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare and the support of EU funding programmes;⁴⁷
- The European Council Recommendation for the adoption of national plans and strategies for ensuring access to high-quality healthcare including through the identifications of Centres of Expertise for the management of rare diseases;⁴⁸

Overall through these mechanisms the Regulation is achieving a balance between incentivising innovation and ensuring post-exclusivity competition in the EU.

For example, orphan medicinal products treating rare diseases such as Multiple Myeloma, Glioblastoma and Gaucher's disease already have several follow-on products authorised for marketing in the EU.⁴⁵

3. Ensuring R&D support at a Member State level

The Orphan Regulation also seeks to ensure the continued support for R&D into rare diseases at a Member State level, by requiring the European Commission to collect, publish and update regularly a detailed inventory of the measures and incentives supporting R&D into rare diseases that are made available by Member States.⁴⁶

Following the introduction of the EU Orphan Regulation, additional policies and actions in the field of rare diseases have taken place at the EU level, including:

- The promotion of EU-wide collaborative initiatives and exchange of policies and best practices through the Rare Diseases Task Force (later replaced by the European Committee of Experts on Rare Diseases, followed by the European Commission Expert Group on Rare Diseases);
- The creation of several international collaboration platforms, such as the E-Rare Consortium which funds transnational collaborative research on rare diseases,⁴⁹ and the International Rare Diseases Research Consortium (IRDiRC) launched in 2011 with the EC and the US NIH as the initiating institutions.⁵⁰
- The creation of several registries of rare diseases aimed at increasing knowledge on rare diseases and developing clinical research.⁵¹

2.2 The patchy status of orphan medicinal product development schemes worldwide

Increasing awareness to the burden of rare diseases has put the issue higher on the public health agenda globally, and various countries around the world have made strides in improving access to treatments for rare diseases by adopting dedicated regulations or national plans.⁵²

However, only a handful of countries have established orphan designation criteria and offer incentives for the development of innovative treatments for rare diseases. Where available (such as Australia, Canada, South Korea, Taiwan

and Switzerland) these incentives mainly focus on expedited approval pathways and limited reduction of regulatory fees, rather than on incentivising the development of treatments towards unmet clinical needs. Indeed, only the EU, US and Japan offer comprehensive product development and R&D incentives and support.

Below Table 3 provides a comparative overview of the incentives for orphan medicinal product development offered in those countries vis-à-vis the major schemes in the US, the EU and Japan.

TABLE 3 Developing an orphan medicine: A critical global challenge without enough support and incentives

	US	EU	Japan	Canada	Australia	South Korea	Taiwan
Exclusivity period (in years)	7	10 (+2 for paediatrics)	10*	None	None	10 (+1 for paediatrics)*	10**
Tax incentives	Yes	At member-state level	Yes	No	No	No	No
Accelerated approval procedure	Yes	Yes	Yes	Yes	No	No	Yes
Waiver of fees	Yes	Yes	Partial	No	Partial	No	No
Discounted Scientific assistance	No	Yes	Yes	No	No	No	Yes
R&D grants	Yes	Yes	Yes	No	No	No	No

* Orphan medicines in Japan and Korea benefit from a 10-year period of data exclusivity, which is inferior to orphan exclusivity, as data exclusivity does not prevent the market entry of competitors who generated their own clinical data.⁵³

** In Taiwan a similar product can be approved for marketing during the market exclusivity period of the first product, if the price of the first product is deemed 'unreasonable'.

Source: Pugatch Consilium (2017)

3 THE IMPACT OF THE EU ORPHAN REGULATION ON ORPHAN DESIGNATIONS AND ORPHAN PRODUCT APPROVALS

Since entering into force in 2000, the number of applications submitted to EMA and the number of orphan designations and orphan product approvals has increased at an exponential rate.

Orphan designations

Figure 3 below shows the number of applications for orphan designation and approval between 2000 and 2017.

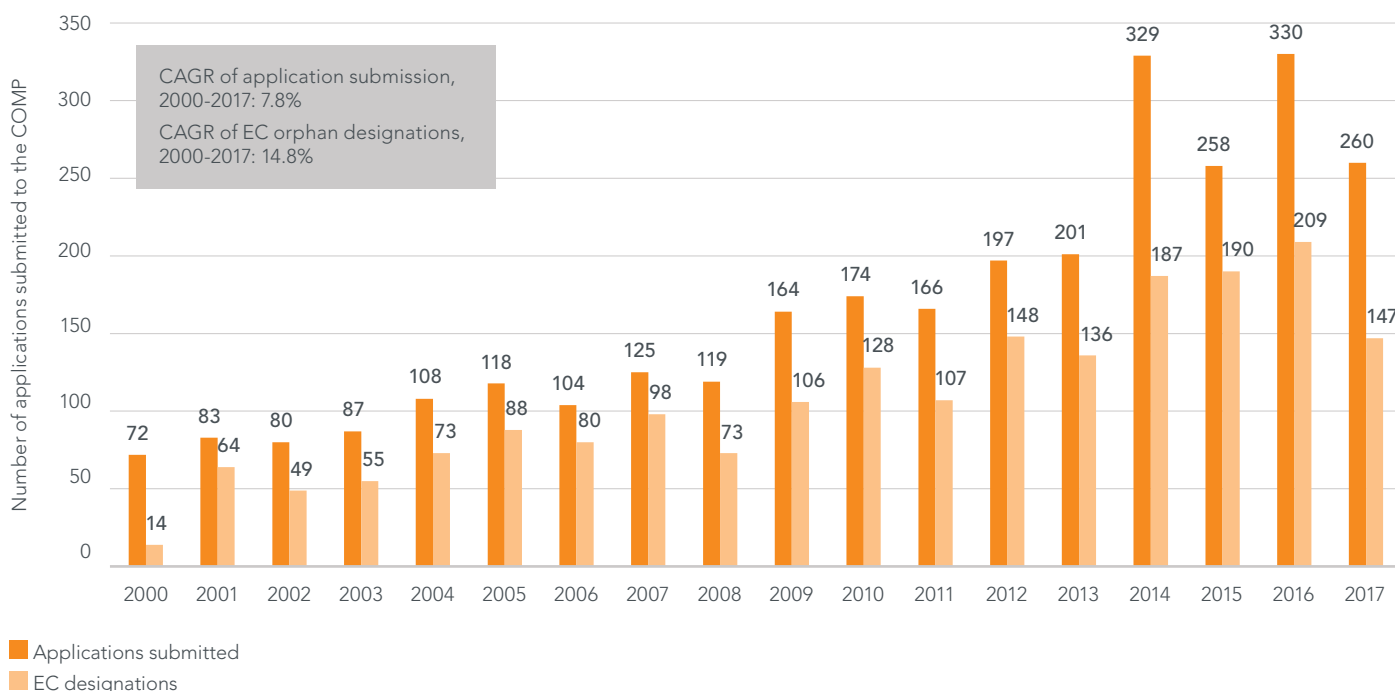
Several insights can be drawn from Figure 3:

- Over the course of its 17 years of existence the EU Orphan Regulation has resulted in 2,975 applications for orphan designations, growing at a CAGR of 7.8%.

- During this period, the annual number of approved designations has grown by a CAGR of 14.8% – double the CAGR of applications submitted; in total, the 2,975 applications have resulted in 1,952 products being designated as orphan.

Evidence from the academic literature provides additional insights: For example, recent studies find that approximately 50% of the approved designations targeted rare conditions that lacked any previously approved treatment in the EU, while

FIGURE 3 Annual rates of applications for orphan designation and approval and COMP opinions, 2000-2017



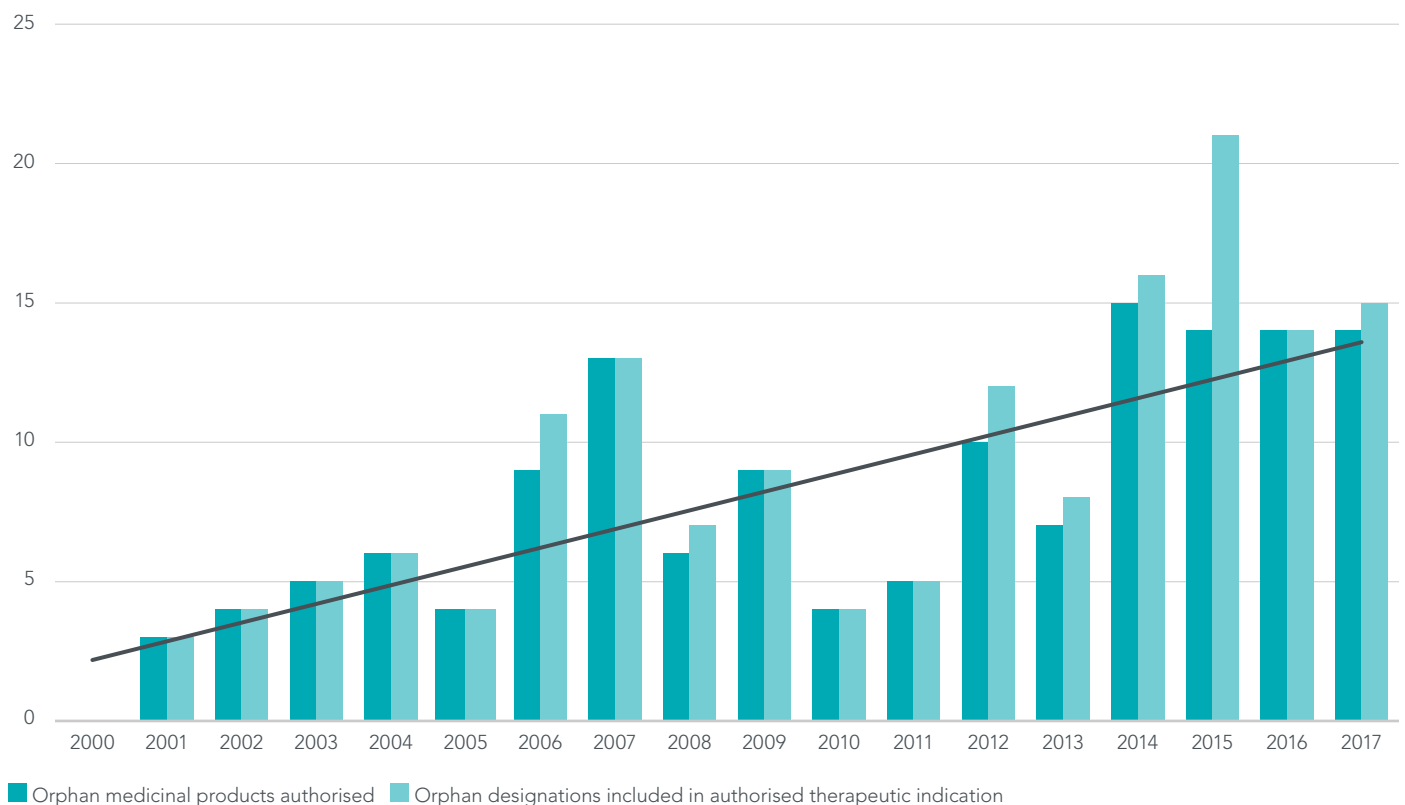
Source: Committee for Orphan Medicinal Products (COMP), meeting report on the review of applications for orphan designation, September 2018, Annex I; analysis: Pugatch Consilium

the rest provided a significant clinical benefit or major contribution to patient care over existing treatments.⁵⁴ Furthermore, the number of rare conditions for which an orphan designation exist in the EU has increased from 200 in 2006 to 370 by the end of 2015, with approximately 60% of the approved orphan designations target conditions with a prevalence of below 1 in 10,000.⁵⁵

Orphan product approvals – general

- Today there are over 150 orphan medicinal products approved by the EMA for over 90 rare diseases – up from only 8 orphan products available in 2000.⁵⁶
- The annual number of orphan product approvals by the EMA has also increased at a steady rate by a CAGR of 10.8% between 2001 and 2017, with some products covering more than one orphan designation (thus treating more than one rare condition).
- Small and Medium Enterprises (SMEs) are responsible for 72% of orphan designations and medicinal products.⁵⁷

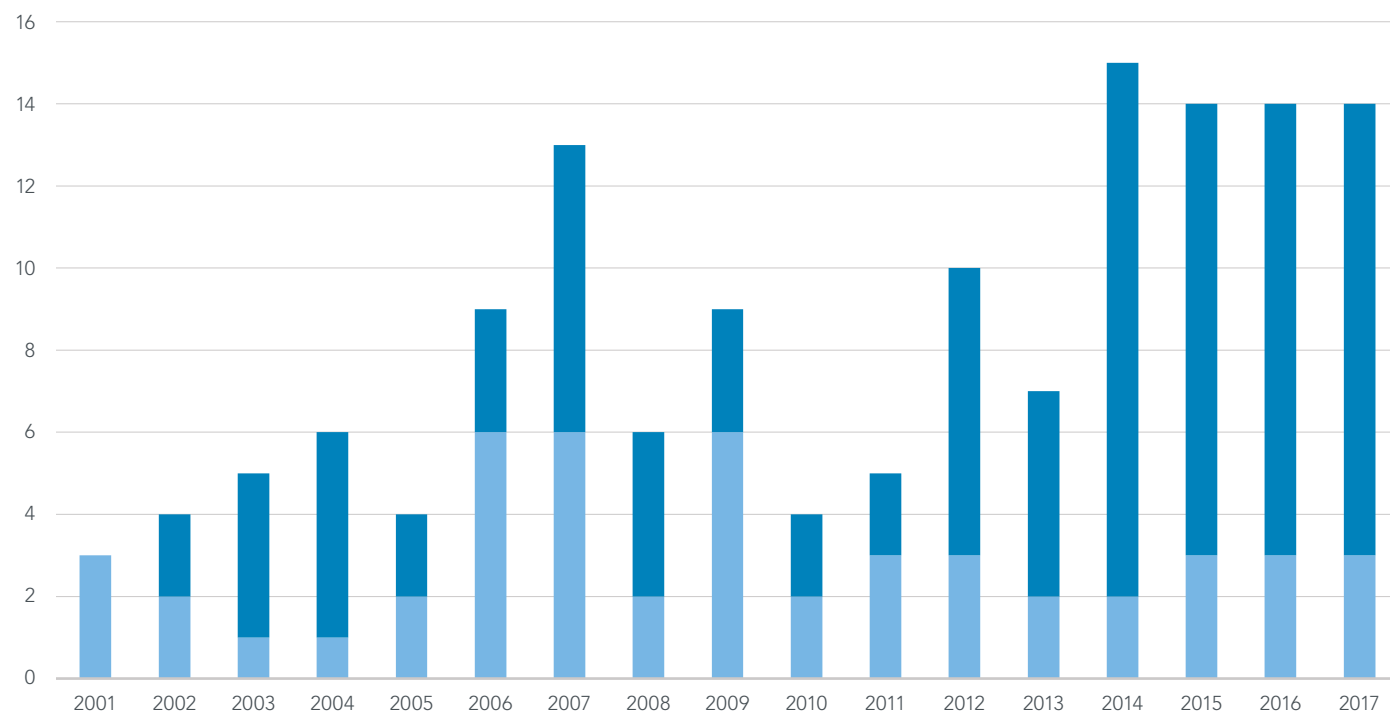
FIGURE 4 Annual rate of approval of orphan medicinal products by the EMA, 2000-2017



Source: Committee for Orphan Medicinal Products (COMP), meeting report on the review of applications for orphan designation, September 2018, Annex I; analysis: Pugatch Consilium

Orphan product approvals – paediatric

FIGURE 5 Annual rate of approval of orphan medicinal products that also treat paediatric populations v. adult populations only, 2000-2017⁵⁸



- Orphan medicinal products authorised for adult populations only
- Orphan medicinal products available for paediatric populations

Source: *Orphanet*, Lists of medicinal products for rare diseases in Europe (European Community marketing authorisation under the centralised procedure), July 2018; analysis: Pugatch Consilium



- As of July 2018, there were 59 orphan medicinal products that also treat children with rare diseases that are approved for marketing in the EU, representing about a third of all orphan products approved in the EU.⁵⁹
- The majority of these orphan medicinal products were authorised in the past decade.
- However, as between 50% to 75% of rare diseases affect children,⁶⁰ more efforts are needed to provide treatments to the paediatric populations.



Professor Meir Pugatch

Managing Director, Pugatch Consilium; IPKM Professor of Valorisation, Entrepreneurship and Management, University of Maastricht, the Netherlands, and former Chair of the Health Systems Administration and Policy Division at the School of Public Health, University of Haifa, Israel.

By offering the right incentives – the extended market exclusivity in particular – the EU Orphan Regulation has succeeded in turning a market with 8 products in 2000 to a market with over 150 products in 2018 – all of which are either first-in-class or bringing a significant clinical benefit

to patients. In my view, this is a clear affirmation to the success of the EU Orphan Regulation in fulfilling its stated purpose of incentivising the research, development and placing on the market of designated orphan medicinal products.

Disclaimer: The views and opinions expressed in the interviews belong solely to the person interviewed and do not purport to reflect the views or opinions of current or past organisations in which the person interviewed is or has been employed in any way.

Looking ahead: What can be improved to increase the number of orphan medicinal products?

The discovery and development of hundreds of treatments for rare diseases was made available through a unique framework of collaboration between researchers and medical experts, patients, funding from EU programmes, industry-led research and development, driven largely by the incentives offered under the EU Orphan Regulation. Advanced genomic research and improved data sharing and collaboration have already resulted in the discovery of genetic mutations and faulty genes responsible for some rare diseases.⁶¹ While progress so far has been substantial, rare diseases continue to pose significant challenges, as 95% of rare diseases still lack an approved treatment.⁶²

As novel approaches continue to be explored for improving the understanding of rare diseases natural mechanisms using cutting-edge technologies within the biomedical sciences, novel approaches supporting this research and development of novel treatments for rare diseases should be examined to promote the translation of the generated knowledge into safe and effective treatments for unmet clinical needs.

Encouraging early academia-industry collaboration

Evidence from the academic literature shows that robust and effective collaboration between the academia and the biopharmaceutical industry is a key driver in the development of novel products for unmet needs.⁶³ This is particularly true for rare diseases in light of the scarcity of knowledge and additional challenges in the R&D stages as outlined in section 1. There is progress to build on including, for example, with respect to cross-border data sharing via the European Reference Networks, Centres of Expertise and professional organisations such as EURORDIS, Orphanet, E-Rare and IRDIC.

Creating dedicated pathways that are based on early multi-stakeholder dialogue and real-world evidence

Generating sufficient clinical evidence for the approval of an orphan medicinal product is extremely challenging, given the scarcity and geographical dispersion of patients. A framework that enables early dialogue between the developers of orphan medicinal products that show promise early in the development stage and regulators within EMA could facilitate more early

access to innovative treatments, while ‘real-world usage data’ supplements the body of evidence generated in the clinical trials stage. The utilisation of early dialogue and the generation of real-world evidence would reduce uncertainties with regards to the evaluated product’ safety and efficacy profile, leading to more informed and effective decision-making process.

Indeed, the EMA has already successfully tested this process through the ‘adaptive pathways’ pilot during 2014-2016, and continues to provide it today.⁶⁴ In addition, the Innovative Medicines Initiative initiated the ADAPT-SMART project which provides the tools and methodologies for the adaptive pathway process.⁶⁵ At a Member State level, multi-stakeholder initiatives such as

TRUST4RD – a Tool for Reducing Uncertainties in the evidence generation for Specialised Treatments for Rare Diseases – facilitate a shared understanding of the challenges faced by manufacturers, regulators, HTA bodies, payers and patient groups in the development and use of real-world evidence to address uncertainties for rare disease treatments.⁶⁶

Creating a dedicated regulatory pathway based on these principles and methodologies, while acknowledging the unique challenges in developing an orphan product (including the substantial costs of generating real-world evidence through patient registries), could both increase the number of approved orphan products as well as shorten their time-to-market.



Johan Van Calster

Managing Director, CLIVAN bvba, Policy and Governmental Affairs Office for Medicinal Products; former Management Board Member of the EMA and former Director General at the Directorate-General for Medicinal Products, the Federal Public Service for Public Health, Food Chain Security and Environment, Belgium.

The ‘adaptive pathways’ programme by the EMA has facilitated the gradual build-up of clinical evidence while enabling early access to innovative products. That is a very good approach. Yet it must go hand-in-hand with the utilisation of real-world evidence through existing and improved cross-border framework and early dialogue

between the developers and the regulators, in order to reduce uncertainties and reach an informed decision-making process that will be highly beneficial for all stakeholders, most importantly for the patients.

Disclaimer: The views and opinions expressed in the interviews belong solely to the person interviewed and do not purport to reflect the views or opinions of current or past organisations in which the person interviewed is or has been employed in any way.



4

THE IMPACT OF THE EU ORPHAN REGULATION ON CLINICAL RESEARCH ACTIVITY INTO RARE DISEASES

Clinical trials serve as an excellent proxy for identifying trends in biopharmaceutical innovation.⁶⁷ Countries that maintain attractive conditions for clinical research – such as sophisticated infrastructure, availability of medical experts and professionals, as well as strong incentives for R&D – see significantly higher levels of clinical trial activity in general and specifically for early-phase, complex trials, and also enjoy the societal and economic benefits associated with clinical research.⁶⁸

Yet most importantly, patients in these countries have better opportunities for early access to cutting-edge treatments which may not be available to them otherwise. Such is the case for many patients with rare diseases.

This sub-section highlights the key findings from an analysis of clinical research activity on rare diseases over the past decade both globally and for Europe (including all EU Member States). The analysis set to examine:

- How the volume and type of clinical research on rare diseases has changed within the EU since the introduction of the EU Orphan Regulation;
- How the volume and type of clinical research on rare diseases has changed in other leading clinical research hubs (both with and without special incentives for orphan medicines) over the same time-period.

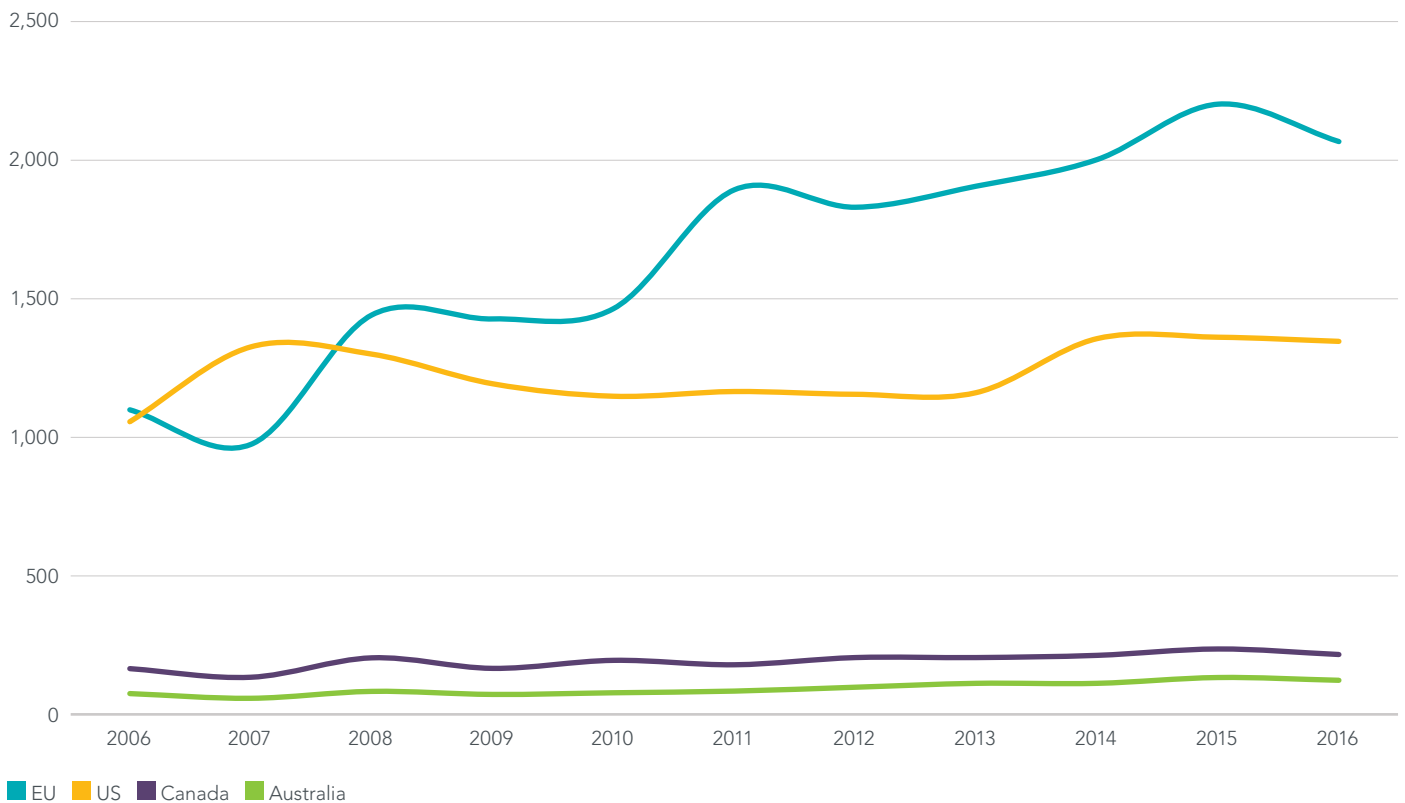
To get an accurate-as-possible depiction of the clinical research activity on rare diseases, this report created a unique dataset of all the clinical trials on rare diseases that are registered in the US National Institute of Health's (NIH) clinical trial register called clinicaltrials.gov.⁶⁹ The dataset was then reviewed in accordance with Orphanet's list of rare diseases,⁷⁰ to ensure compatibility with current European definitions of rare conditions.⁷¹ The analysis measures clinical trial activity by looking at the number of new trials initiated annually in the countries / regions in focus.

The EU has seen the strongest surge in new clinical trials on rare diseases

- Global activity of clinical trials on rare diseases has increased by 68% between 2006 and 2016, rising from 3,100 clinical trials targeting rare diseases in 2006 to over 5,200 clinical trials targeting rare diseases in 2016.⁷²
- On a regional scale, the EU has seen **the strongest growth** in clinical research on rare diseases since the mid-2000s: Annual activity has increased by 88% between 2006 and 2016.

- At the same time, otherwise leading clinical research hubs such as Canada and Australia (where no special incentives for orphan medicinal product development are in place) witnessed a decade-long stagnation.

FIGURE 6 New clinical trials on rare diseases, selected economies / region, 2006-2016

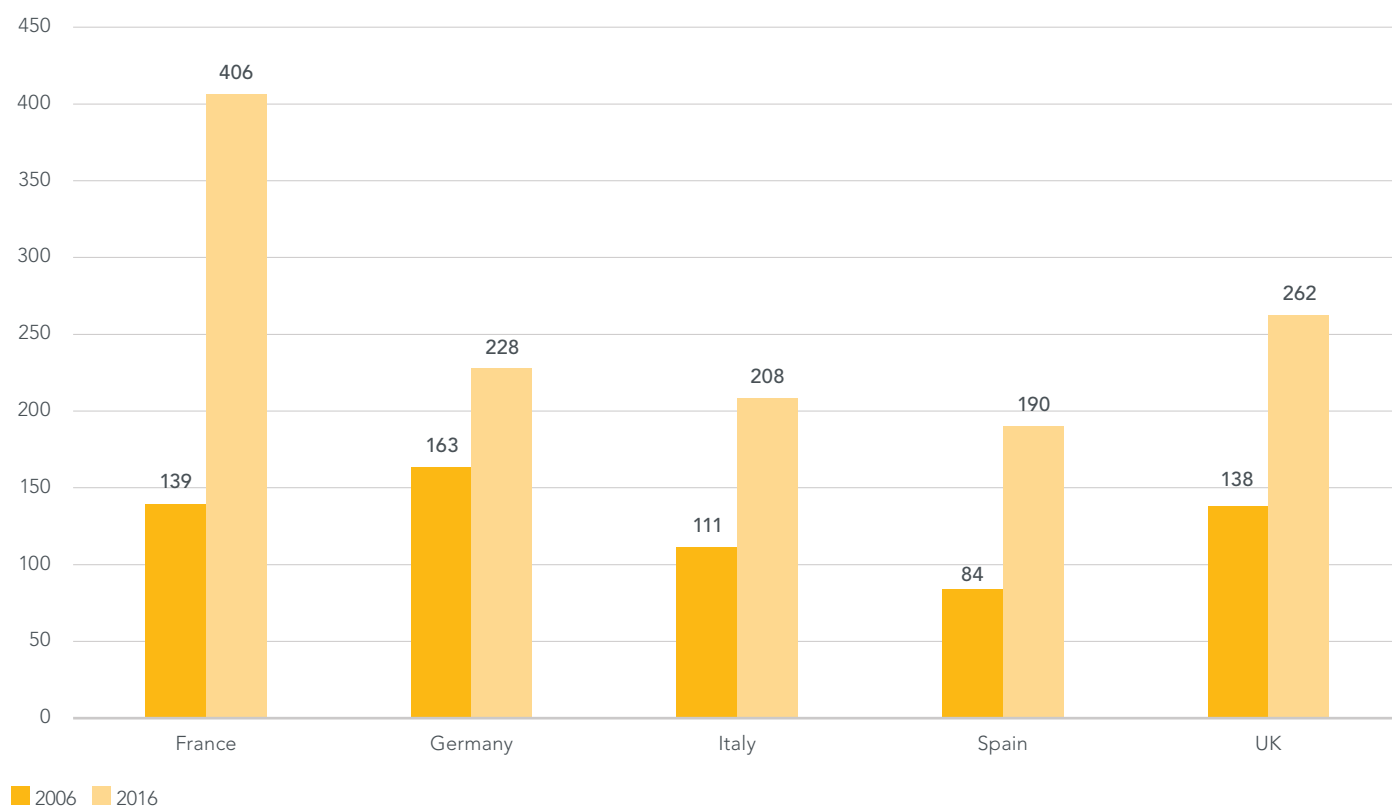


Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

The EU-5 countries play a leading role in driving research into unmet clinical needs

- The EU-5 countries (UK, France, Germany, Spain and Italy) experienced an even bigger increase of 104% in clinical trial activity on rare diseases between 2006 and 2016, with France experiencing the biggest increase of 192%, followed by Spain (126%), the UK (89%), Italy (87%) and Germany (40%) – although Spain remains the lowest among the EU-5 in terms of activity.

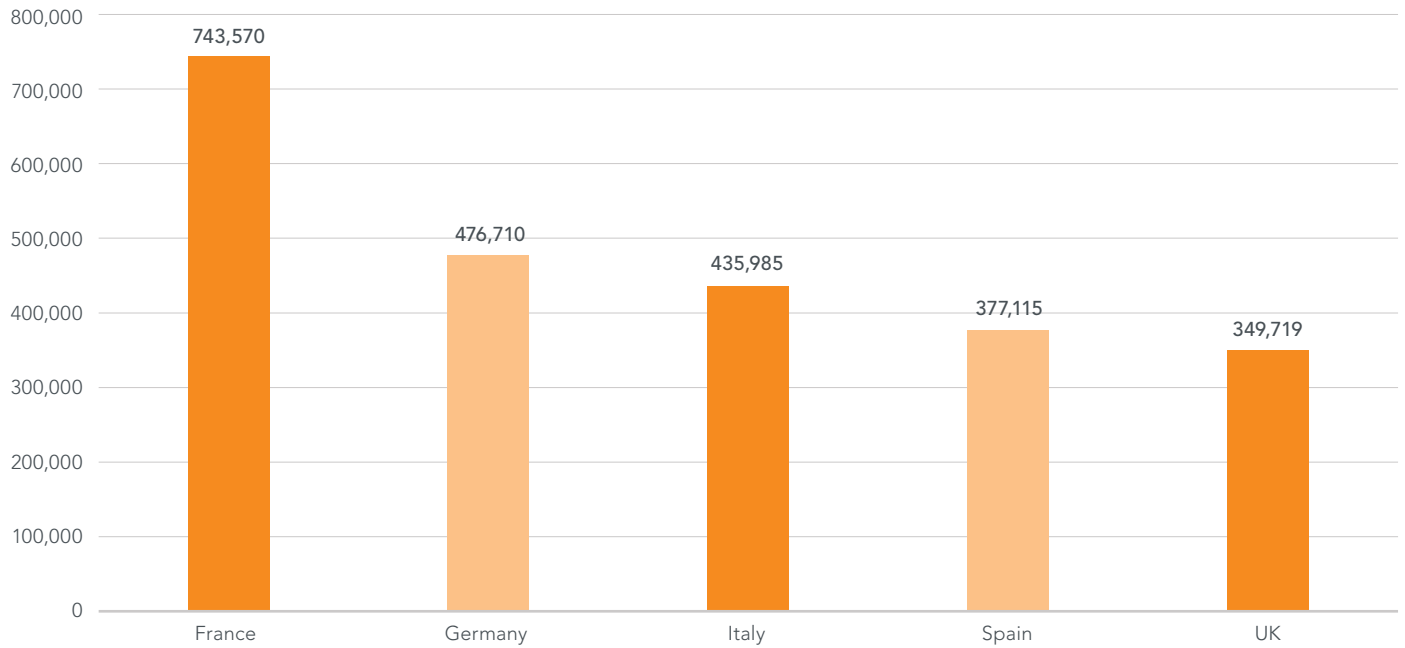
FIGURE 7 New clinical trials on rare diseases in the EU-5 countries, 2006 v. 2016



Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

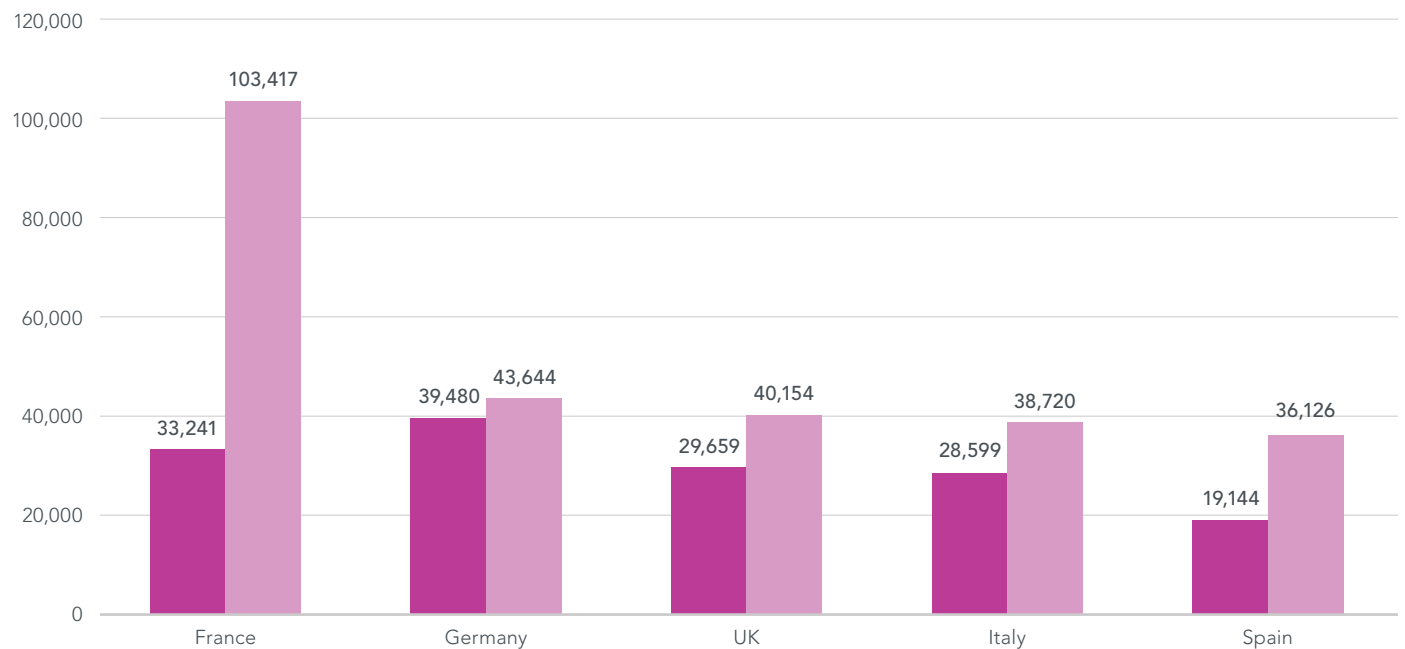
The EU-5 countries are also regional leaders in providing rare diseases patients with early access to potential treatment through clinical trials

FIGURE 8 Enrolment rate for clinical trials on rare diseases in the EU-5 countries, 2006-2016



Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

FIGURE 9 Enrolment rate for clinical trials on rare diseases in the EU-5 countries, 2006 v. 2016

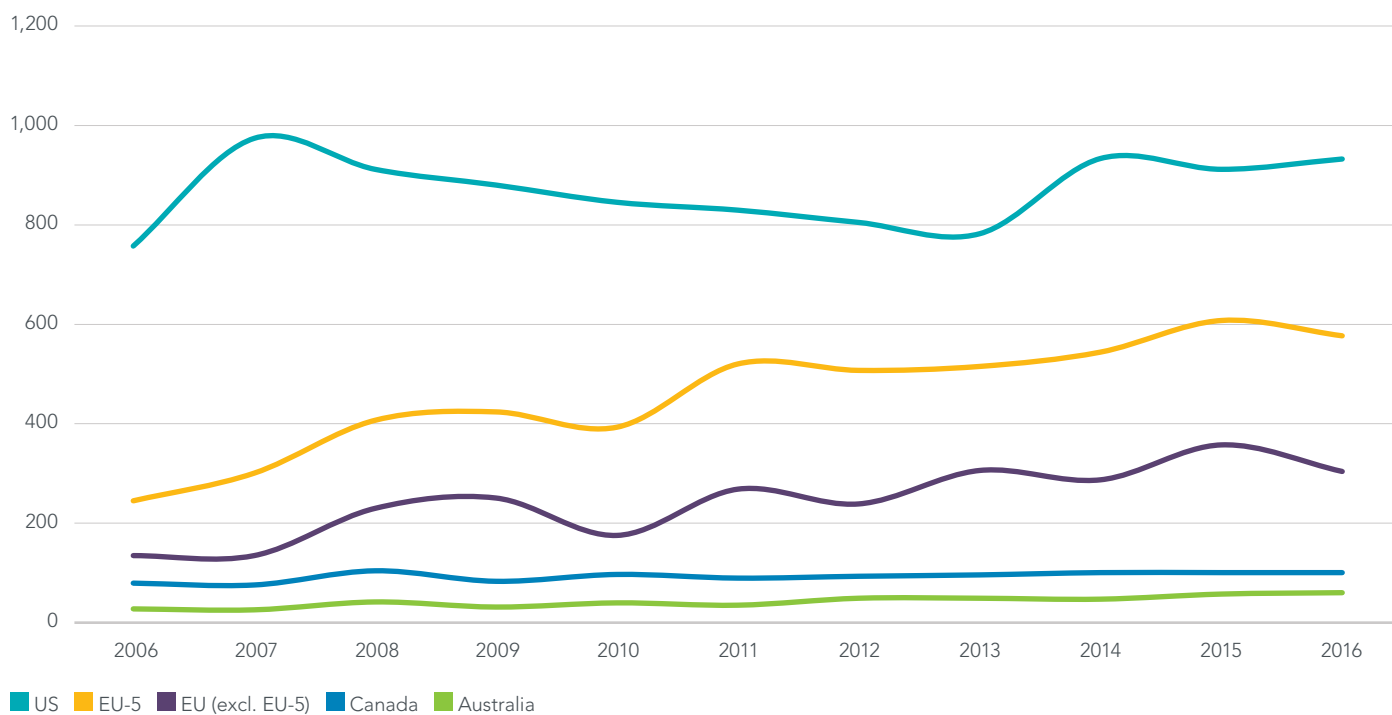


■ Enrolment rate for clinical trials on rare diseases, 2006 ■ Enrolment rate for clinical trials on rare diseases, 2016

Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

- Some 2.37 million patients were enrolled to clinical trials on rare diseases in the EU-5 countries alone between 2006 and 2016.
 - France has seen the largest increase not only in the number of new trials on rare diseases but also in the number of patients enrolled to these trials: In 2016 over 103,000 patients were enrolled to new clinical trials on rare diseases in France – more than 200% compared to enrolment in 2006.
 - Enrolment in the remaining four countries ranges between 40,000 to 45,000 rare diseases patients per year.
- EU Member States – and particularly the EU-5 countries – also play an increasing role in exploring novel treatments for rare diseases**
- The number of early-phase clinical trials on rare diseases in the EU has increased from 378 in 2006 to 883 in 2016, an increase of 134% - higher than the overall growth of clinical trials in the EU during that period.
 - This increase is similar for the EU-5 countries as well as for other EU Member States, indicating that as a region the EU is playing an increasing role in supporting innovative R&D into new, unmet needs. Indeed, nearly € billion of funding were made available for research into rare diseases during the past decade under the 7th Framework Programme, Horizon 2020 and E-Rare's Joint Transnational Calls.⁷³
 - And here too, Canada and Australia which otherwise are playing a lead role in driving early-phase research yet offer no special incentives for orphan medicinal product development, are not seeing a significant (or even mild) increase in early-phase clinical trial activity for rare diseases.

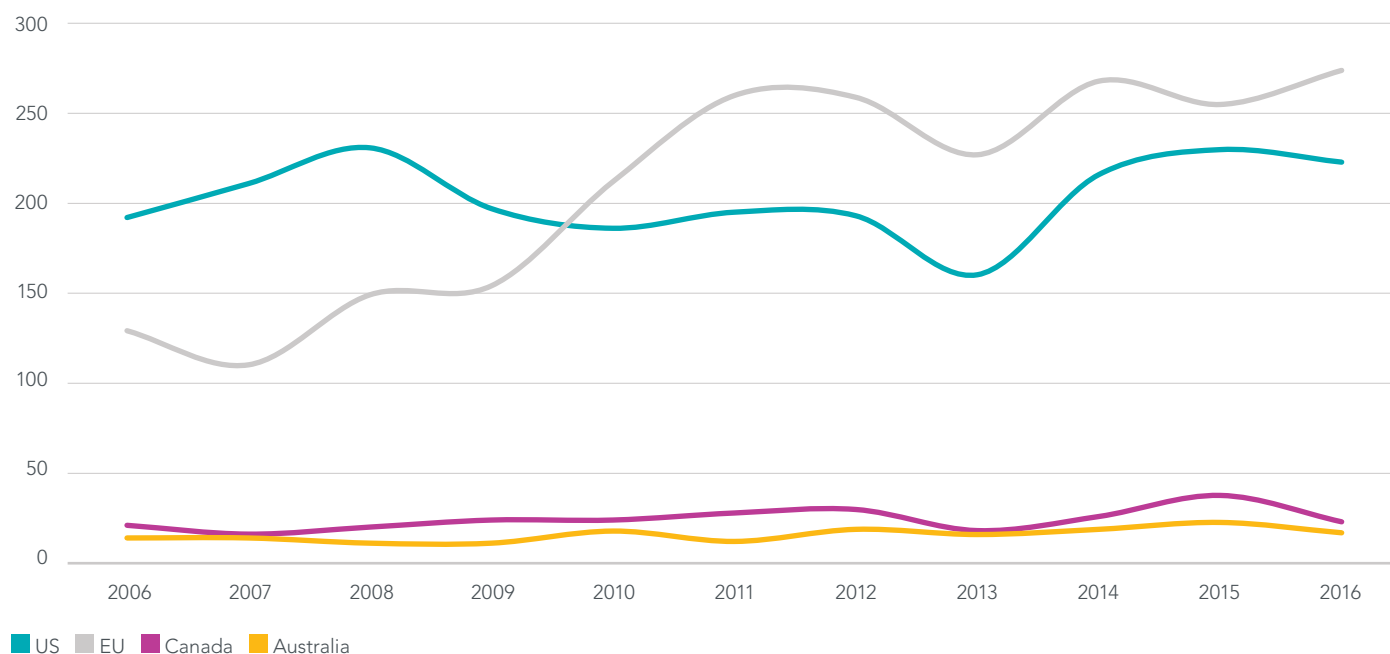
FIGURE 10 New early-phase clinical trials on rare diseases, selected economies / region, 2006-2016



Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

The EU and the US are spearheading R&D of biological treatments for rare diseases

FIGURE 11 New clinical trials on rare diseases using biologic medicines, selected economies / region, 2006-2016



Source: *Clinicaltrials.gov*, 2018; analysis: Pugatch Consilium

- Biologic medicines have revolutionised the treatment of many life-threatening and rare diseases, by slowing the progress of or even preventing diseases, leaving healthy cells unaffected and generally causing fewer side effects.
- Similarly to its role in supporting early research into rare diseases, the EU is today also a global leader in supporting clinical research on biologic medicines for rare diseases: Between 2006 and 2016 the EU experienced a 112% increase in the number of clinical trials on biologic medicines, surpassing even the US in annual clinical trial activity on biologic medicines since 2010.
- And just as shown above for the general clinical trial activity and specifically for early-phase research, Canada and Australia, which offer no special incentives for orphan medicinal product development, remain relatively static with very low activity of only 20-30 clinical trials on biologic medicines for rare diseases.

Looking ahead: Maintaining momentum and driving clinical research on rare diseases to new horizons

Looking at the increase in clinical research activity (both generally as well as in complex early-phase and biologic research) on rare diseases, the EU Orphan Regulation can be unequivocally viewed as a success. EU Member States are spearheading the cutting-edge research on rare diseases – despite the significant clinical challenges – and are experiencing the associated benefits of improving local researchers and physicians’ expertise, increasing high-skill employment, and, most importantly, providing their patients with early access to potential novel treatments. In contrast, as this study shows, other countries such as Canada and Australia (which otherwise are highly competitive and attractive hubs for clinical research but do not offer special incentives for orphan medicinal product development) have experienced a decade-long stagnation and even reduction in clinical trial activity on rare diseases.

Yet there is no room for complacency, given the fact that more than 90% of known rare diseases still lack treatment. Furthermore, a clear discrepancy in activity levels of clinical trials on rare diseases exists between EU Member States, resulting in unequal access to research on potential new treatments. Efforts at both the EU and Member States levels should continue to capitalise on the progress achieved so far and encourage more R&D, into unmet needs.

Harnessing the potential of advanced technologies to improve R&D productivity

The field of clinical research does not remain unresponsive to technological advancements. Big Data mining, bioinformatics and Digital Health

platforms are already changing the healthcare landscape, and hold tremendous potential to increase R&D productivity. Yet the utilisation of new ways and tools for effective data analysis and generation of clinical evidence is not enough in itself. Efforts should also be directed towards the harmonisation of clinical trial design, execution and data sharing, as well as towards enabling shared dialogue and collaboration between all stakeholders, in early stages of the research. These would enable the establishment of the safety and efficacy profiles of potential treatments early in the development process, thus increasing productivity as well as shortening the time to market for promising orphan products.



Robert Madelin

Chairman & Partner, Foresight International Policy and Regulatory Advisers (FIPRA) International; former Senior Adviser for Innovation, Director General for Communications Networks, Content and Technology (CONNECT) and Director General for Health and Consumer Policy (SANCO) at the European Commission.

We now have the enabling infrastructure for cross-border collaboration and pan-European data sharing, for example through the European Reference Networks, yet we are still behind the

curve in utilising our abilities to promote cutting-edge research even further, to the benefit of all stakeholders involved, most importantly the patients.

Disclaimer: The views and opinions expressed in the interviews belong solely to the person interviewed and do not purport to reflect the views or opinions of current or past organisations in which the person interviewed is or has been employed in any way.

Increasing Member States' involvement in supporting clinical research on rare diseases, for example through the European Reference Networks

As discussed throughout this study, the EU played, and continues to play a key role in driving collaborative research into rare disease through the EU Orphan Regulation, the EU Cross-Border Healthcare Directive, pan-European organisations, and the recent launch of 24 dedicated European Reference Networks, which encompasses over 300 hospitals and 900 specialised teams, and utilises various instruments with the purpose of ensuring proper access to specialised healthcare across the EU.⁷⁴

The effective utilisation of the advanced research infrastructure for the benefit of all EU patients with rare diseases requires the commitment and active participation of EU Member States in supporting EU-wide research coordination efforts through the European Reference Networks (ERNs), creating national databanks and patient registries to facilitate outreach and recruitment, and encourage more local R&D activity – particularly clinical research – by offering incentives at a national level, such as tax reductions for clinical trials, fee waivers, and streamlined regulatory process for clinical research.



Bernard Merkel, PhD

Special Advisor for healthcare issues, Foresight International Policy and Regulatory Advisers (FIPRA), Belgium; former Head of Health Strategy at the European Commission.

The EU Orphan Regulation has played a key role in promoting the conceptualisation of rare diseases as a European issue par excellence. Conjointly with a series of initiatives at both the pan-European and Member State levels, the EU Orphan Regulation demonstrated the genuinely important role that the European Commission has played in promoting public health in the field of rare diseases for the entire European Union. This thinking drove later initiatives such as the Cross-Border Healthcare Directive, and

the establishment of the European Reference Networks. In addition to the health and social benefits there was the expectation that the incentives would support the development of the European research-based industry. In my view, the thinking behind the EU Orphan Regulation and additional initiatives made in the field of rare diseases in the EU constitute an excellent example of the solidarity and cohesiveness that constitute a major added value of the EU Orphan Regulation.

DISCLAIMER: THE VIEWS AND OPINIONS EXPRESSED IN THE INTERVIEWS BELONG SOLELY TO THE PERSON INTERVIEWED AND DO NOT PURPORT TO REFLECT THE VIEWS OR OPINIONS OF CURRENT OR PAST ORGANISATIONS IN WHICH THE PERSON INTERVIEWED IS OR HAS BEEN EMPLOYED IN ANY WAY.

5 MORE RESEARCH, MORE DESIGNATIONS, MORE PRODUCTS, BUT WHAT ABOUT ON-THE-GROUND PATIENT ACCESS?

As the preceding section has demonstrated, the scale of the increase in approved orphan designations and products in the EU since 2000 strongly suggests that the EU Orphan Regulation has succeeded in encouraging the development of orphan medicinal products. But market approval is only part of the story. How many of these EMA approved orphan products are actually available to patients across the EU?

In its assessment report of 2006, the European Commission cites a survey conducted by EURORDIS which found that for a sample of 12 orphan products approved by December 2003 only one Member State demonstrated the availability of the entire sample, while only half of the sample or less were available in the rest of the then-25 EU Member States.⁷⁵ The report concludes that:

The full benefits of the EU orphan regulations require optimal synergies between action on Community and on Member State level. **Incentives at the European Union level need to be translated into rapid access of patients to the new products throughout the entire Community** and they need to be supplemented by incentives at Member States level. In this regard, the past experience was not entirely satisfactory.⁷⁶ [emphasis added]

With now over 150 orphan products authorised for marketing in the EU, this sub-section analyses the current rates of availability of orphan products by building on evidence from recent surveys that examined:

- a) The number of orphan products reimbursed in a given Member State; and
- b) The duration from the product's date of marketing authorisation to the date of receiving public reimbursement in a given Member State; or
- c) The differences between patients with rare diseases and the general population of patients regarding the level of reimbursement.



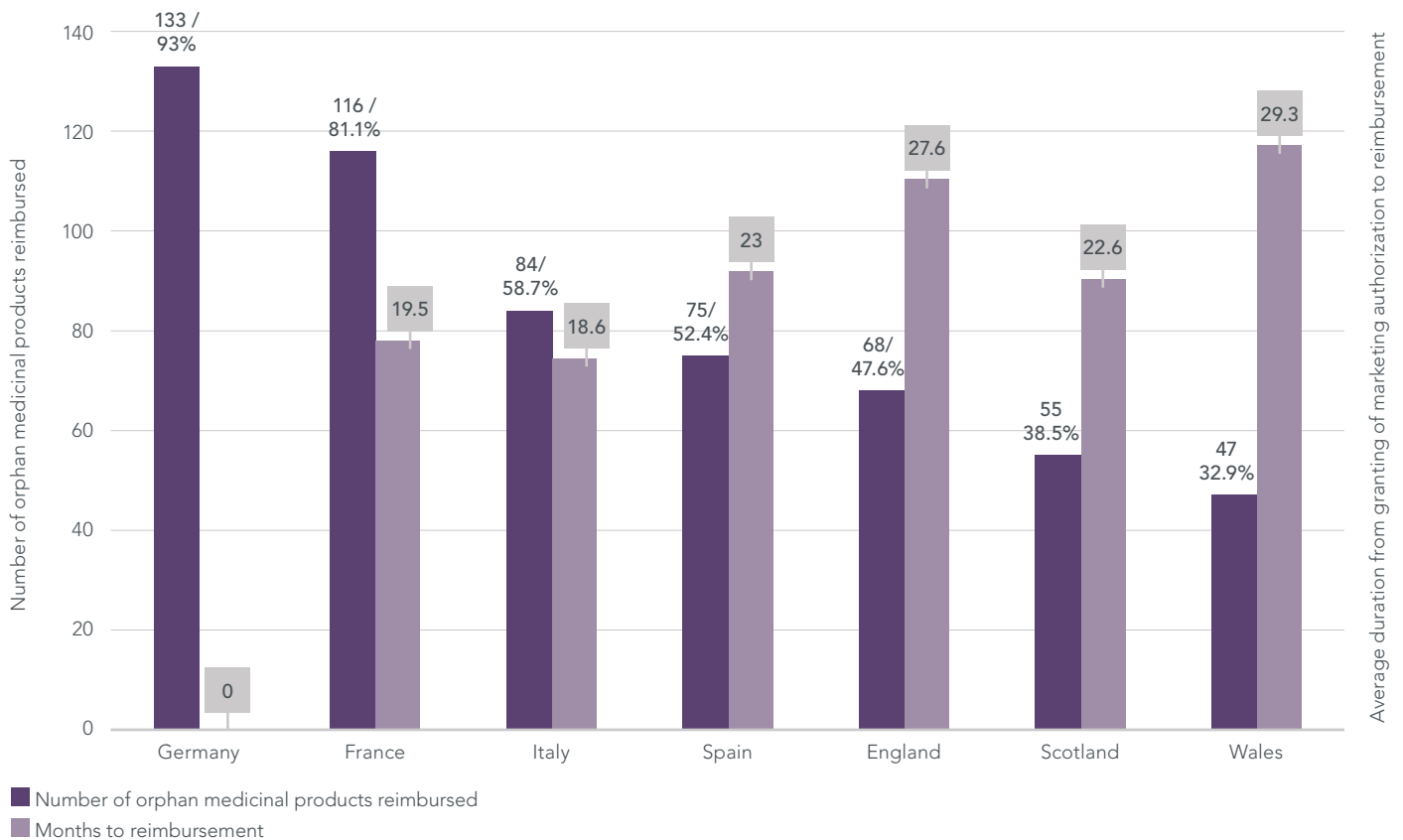
Access to orphan medicines still varies greatly between Member States

A 2017 study by the OHE compared access to 143 orphan products that were approved for marketing in the EU between 2000 and 2016 (May 31st) across the EU-5 countries (including a division between England, Scotland and Wales that comprises the UK).⁷⁷ Overall the study found that:

- Access to authorised orphan products through public reimbursement varies substantially between the sampled Member States, ranging from 93% in Germany to 33% in Wales, as is evident in the above Figure 14.

- The average duration between the granting of marketing authorisation by the EMA and reimbursement decision by the national authority is 23.4 months – nearly two years.⁷⁸
- That duration is also considerably longer for orphan medicines when compared to non-orphan medicines:
 - For example, in the UK the median number of months between the marketing authorisation and the first NICE appraisal is 20.2 months for orphan medicines compared to 12.7 months for non-orphan medicines.

FIGURE 12 Access to orphan medicines in the EU-5 countries: Rates of and time to reimbursement

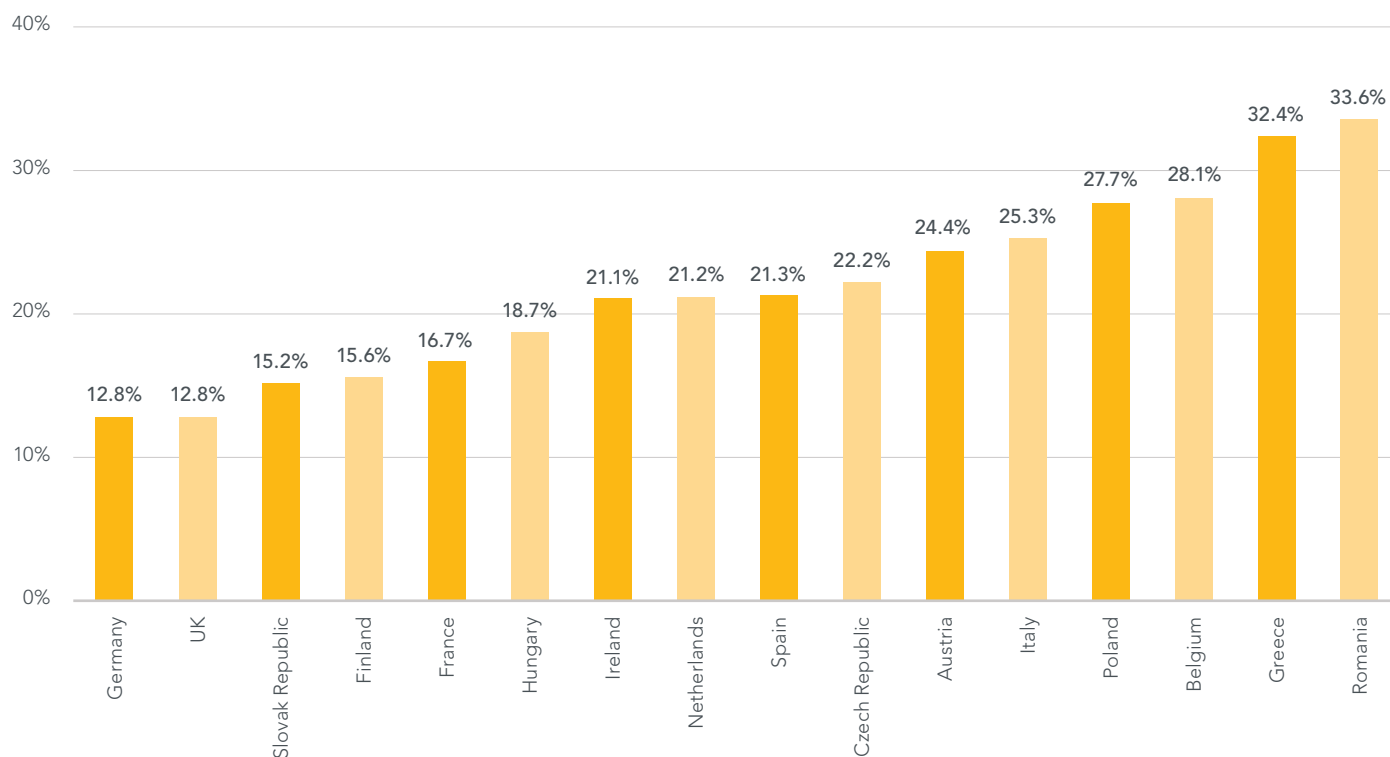


Source: Zamora et Al. (2017). Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries, Office of Health Economics.

Insufficient reimbursement and long delays are viewed as the main obstacles for access

- The EURORDIS Access Campaign survey,⁷⁹ which brings the views of 1,943 respondents from 31 European countries, reveals that 44% of respondents reported a worsening of their access to treatment between 2014 and 2016.
- Insufficient reimbursement of orphan medicines is perceived as one of the major barriers to receiving proper treatment in almost all EU Member States, indicating a *postcode lottery* in access to needed treatments for EU patients with rare diseases.
- The gap between EU Member States is substantial: The share of respondents citing insufficient reimbursement is almost 3 times higher in Greece and Romania compared to Germany and the UK.
- The five EU Member States where the share of respondents citing insufficient reimbursement is highest – Romania, Greece, Belgium, Poland and Italy – also have the highest share of respondents citing ‘medicines’ as the type of care they experience difficulties in.⁸⁰

FIGURE 13 EURORDIS Access Campaign: Rates of patients with rare diseases reporting insufficient reimbursement as an obstacle to receiving proper treatment, 19 European countries, 2016



Source: EURORDIS Access Campaign, country results, 2016; analysis: Pugatch Consilium

EU patients with rare diseases receive unequal care as a result of insufficient reimbursement and long delays

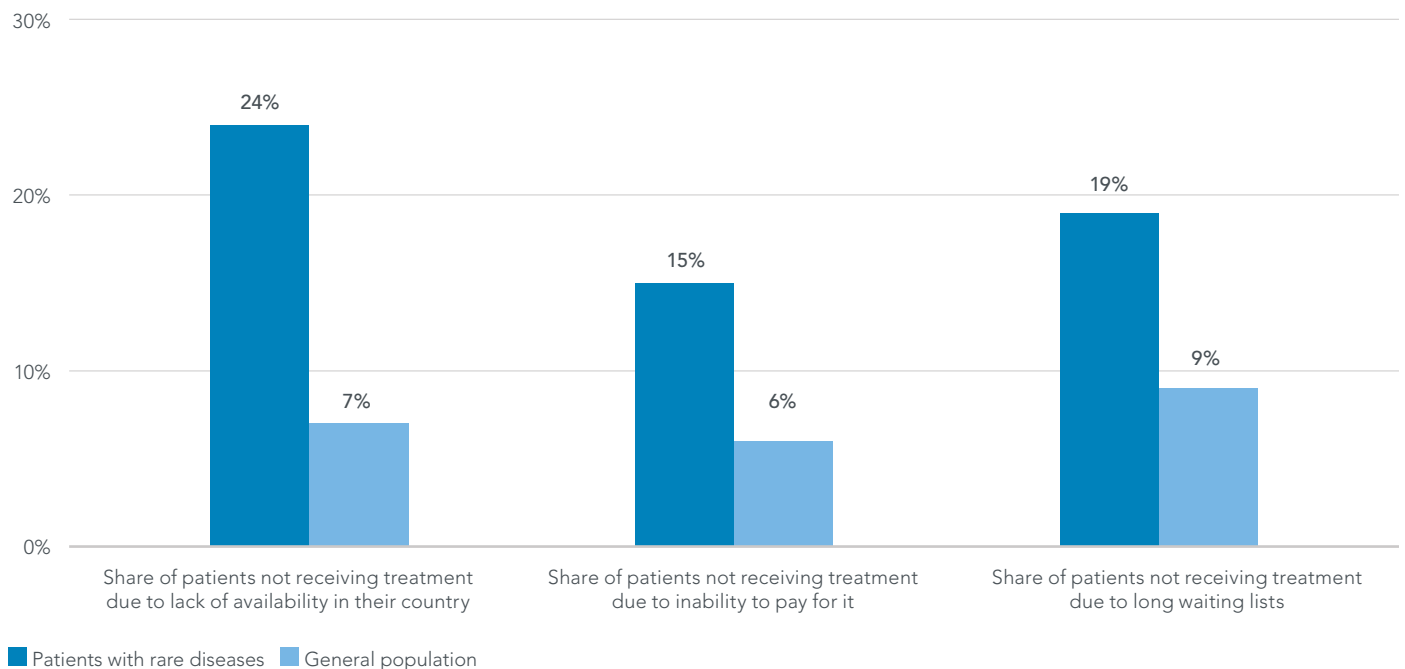
The EURORDIS Rare Barometer survey⁸¹ shows a significant gap in access to treatment between patients with rare diseases and the general population.

The EURORDIS Rare Barometer survey of 2017, which brings the views of 1,350 respondents from 21 European countries, complements the findings of the Access Campaign, by emphasising the discrepancy in access to treatment between patients with rare diseases and the general population.

Looking ahead: what can be done to ensure that EU patients with rare diseases receive timely and equitable access to treatments?

The EU Orphan Regulation has succeeded remarkably well in promoting research into rare diseases and incentivising the development of orphan medicinal products. However, the last step – providing patients with rare diseases with actual access to these medicines – is at the sole responsibility of the Member States. Studies show that access to orphan medicinal products is hampered by insufficient reimbursement and long delays, resulting in unequal access to care for patients with rare diseases. To address this barrier, more efforts and forward-thinking are required at both the EU level and that of individual Member State.

FIGURE 14 EURORDIS Rare Barometer survey: Differences in access to treatment between patients with rare diseases and the general population



Source: EURORDIS Access to treatment: unequal care for European rare disease patients - A Rare Barometer survey, February 2017; No. of respondents: 1,350, from 21 European countries; analysis: Pugatch Consilium

Reducing uncertainties and long approval processes by harmonising the clinical aspects of HTA

Given the considerable differences in the duration of the reimbursement decision process between EU Member States, efforts could be directed towards the harmonisation of the clinical aspects of the HTA processes for orphan medicinal products across EU Member States. The utilisation of early dialogue and the generation of real-world evidence (as discussed in the former sections) would reduce uncertainties with regards to the evaluated product's safety and efficacy profile, leading to more informed and effective decision-making process. Indeed, a proposal for a Regulation on HTA has been published earlier this year by the EC, opting for early dialogue and a legislative framework for joint assessment of the clinical aspects of the HTA.⁸² The EC estimates that this initiative would have a significant social and economic impact realised through reduced duplicative efforts and cost savings, expedited market access to innovative products (by 2 to 6 weeks) as well as an improved decision-making process and predictable regulatory process with regards to generation of clinical evidence.⁸³ This presents a unique opportunity for promoting healthcare system sustainability and better public health throughout the EU.

However, in order to create an effective framework for collaboration that would eliminate the delays caused by duplicative efforts and differences in technical capacity at a national HTA level, while retaining Member States' mandate in performing their own assessments for guiding pricing and reimbursement decisions, the joint HTA process should be limited to the clinical aspects alone, while providing the opportunity for early dialogue on clinical data requirements and comparator selection for the regulatory approval and joint assessment, through a joint scientific consultation.

Exploring novel funding approaches that secure access within budgetary confinements while fostering innovation

The core values that guided the EU Orphan Regulation and Cross-Border Healthcare Directive were humanitarian solidarity and communal cohesiveness. Where lack of affordability denies access to treatment for EU patients with rare diseases, collective efforts should be marshalled to overcome this barrier. Novel funding models at the EU level that are based on agreed principles (such as, for example, performance-based funding) and actual needs in individual Member States may offer a solution to patients with rare diseases in EU Member States while continuing to incentivise the development of more orphan treatments for unmet clinical needs.



Johan Van Calster

Managing Director, CLIVAN bvba, Policy and Governmental Affairs Office for Medicinal Products; former Management Board Member of the EMA and former Director General at the Directorate-General for Medicinal Products, the Federal Public Service for Public Health, Food Chain Security and Environment, Belgium.

Equitable access to treatment for patients with rare diseases is the third pillar of the EU Orphan Regulation. The gaps in access to treatments between EU-Member States – particularly vis-à-vis the relative success of the Orphan Regulation in driving research and development of orphan medicines – should capture the focus of improvement efforts. The orphan designation and marketing authorisation of orphan medicines

are only the first steps; these treatments must be accessible by EU patients following a uniform Health Technology Assessment (HTA), conducted under clear guidelines and principles of social responsibility, and whose outcomes are preferably accepted by all the Member States.



CONCLUSION

The purpose of this report has been twofold. First, to assess whether the EU Orphan Regulation has accomplished its aim of incentivising R&D into rare diseases and the development and introduction of new products and therapies onto the EU market. Second, to examine some of the current and future big challenges and questions about R&D and new product development for rare diseases.

On whether or not the Orphan Regulation has achieved its stated objectives the evidence is quite clear: **In its first evaluation of the EU Orphan Regulation accomplishments in 2006 the EC concludes that “the orphan legislation in the EU has far exceeded initial expectations”.**⁸⁴ 12 years on, the EU Orphan Regulation can unequivocally be viewed as a success: Over 150 orphan medicinal products approved by the EMA for over 90 rare diseases (up from only 8 orphan products available in 2000), and the EU is spearheading global clinical research on rare diseases, providing early access to potential novel treatments for hundreds of thousands of EU patients with rare diseases each year. The overall progress achieved in the EU in the field of rare diseases in the past two decades is a perfect example of the solidarity and communal cohesiveness that continue to drive the European Union.

Yet there is no room for complacency: More than 90% of known rare diseases still lack treatment, and EU patients with rare diseases continue to experience unequal care due to a lack of real-world access. Indeed, evidence from several studies reveal substantial discrepancies between EU Member States in the number of orphan medicinal products available through public reimbursement, and patients report insufficient reimbursement and long delays in market entry in many EU countries and at significantly higher rates compared to the general population.

Thus, while the EU Orphan Regulation has in fact played, and continues to play a key role in driving the research and development of orphan medicinal products, national P&R policies act as barriers to getting novel orphan products to patients who need them. That is despite the

fact that the impact of orphan medicines on pharmaceutical spending in Europe is estimated at 4.6%⁸⁵ – less than the prevalence estimates of patients with rare diseases in Europe!

Building on recent developments and insights drawn from interviews with established experts and thinkers within the rare disease community, the report offers potential solutions and approaches for capitalising on the progress achieved so far and encouraging more R&D, into unmet needs, accessible by all EU patients with rare diseases.

What stands out most prominently from the findings of this report and the ideas put forth by the pool of experts interviewed is that considerable progress has been achieved under the EU Orphan Regulation and additional initiatives in the field of rare diseases in the EU. Through collaborative efforts and commitment from all stakeholders involved – the scientific and healthcare communities, the biopharmaceutical industry, regulators, payers, patient organisations and the patients themselves - novel approaches and new pathways can be explored, evaluated and utilised, leading to the development of more treatments and ensuring that patients with rare diseases will receive the timely and equitable access to care they deserve.

NOTES

- 1 European Commission (2006) Commission staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained.
- 2 The TRUST4RD initiative was presented at The European Health Forum Gastein in October 2018. A final consensus paper will be published in 2019.
- 3 EURORDIS, "Rare Diseases: understanding this Public Health Priority, November 2005, https://www.eurordis.org/IMG/pdf/princeps_document-EN.pdf.
- 4 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, Article 3.1.a.
- 5 Sec. 526 Of The Federal Food, Drug, And Cosmetic Act, <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm>.
- 6 Intractable (referred to in Japanese as 'Nambyo') diseases are conditions without clear cause and treatment that develops into chronic disability and whose diagnosis may depend on the level of healthcare and the social state of affairs of a country at that time. For the full definition see the Japan Intractable Disease Information Center, "What is an Intractable Disease?" (accessed March 2017), <http://www.nanbyou.or.jp/english/index.htm>.
- 7 EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf.
- 8 EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf.
- 9 Stephen C. Groft (2016) "Global View of the Rare Diseases Field", ICORD 11th Annual Conference, October 2016, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/03/WC500164162.pdf.
- 10 EC/IRDIRC (2014), "EU Research Funding for Rare Disease Research", March 2014, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/03/WC500164162.pdf.
- 11 EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf.
- 12 Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- 13 EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf; Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- 14 Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- 15 EURORDIS, Juggling Care and Daily Life: The Balancing Act of the Rare Disease Community, http://download2.eurordis.org/rbv/juggling_care_and_daily_life.infographic_final.pdf.
- 16 Ibid.
- 17 Ibid.
- 18 Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- 19 See: PhRMA, A Decade of Innovation in Rare diseases: 2005-2015, http://phrma-docs.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf?__hstc=110588826.b957993a50e7cecca255597a564b426a.1491563043494.1491563043494.1491563043494.1&__hssc=110588826.1.1491563043494&__hsfp=2010045186.
- 20 FDA News Release, FDA grants accelerated approval to first drug for Duchenne muscular dystrophy, 19.9.2016, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm>.
- 21 FDA News Release, FDA approves first drug for spinal muscular atrophy, 23.12.2016, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534611.htm>.
- 22 See: PhRMA, A Decade of Innovation in Rare diseases: 2005-2015, http://phrma-docs.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf?__hstc=110588826.b957993a50e7cecca255597a564b426a.1491563043494.1491563043494.1491563043494.1&__hssc=110588826.1.1491563043494&__hsfp=2010045186.
- 23 See for example: Lichtenberg, F. (2014). "The impact of pharmaceutical innovation on disability days and the use of medical services in the United States, 1997-2010", *Journal of Human Capital*, Vol. 8, No. 4.; Carls, G. et al, (2012). "Impact of Medication Adherence on Absenteeism and Short-Term Disability for Five Chronic Diseases", *Journal of Occupational & Environmental Medicine*, Vol. 54, Issue 7.; Santerre, R.E. (2011). "National and International Tests of The New Drug Cost Offset Theory", *Southern Economic Journal*, Vol. 77, No. 4, pp. 1042.; Roebuck, M. et al. (2011). "Medication adherence leads to lower health care use and costs despite increased drug spending", *Health Affairs*, Vol. 30, No. 1, pp. 91-99.
- 24 Stephen C. Groft, (2016). "Global View of the Rare Diseases Field", ICORD 11th Annual Conference, October 2016, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/03/WC500164162.pdf.
- 25 Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J & Garau, M. (2017). Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. Office of Health Economics (OHE) Consulting Report.
- 26 See for example: Commission of the European Communities, Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained, p. 9, Brussels, 20.6.2006, https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_en_06-2006_en.pdf; Zamora et Al. (2017). Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries, Office of Health Economics; EURORDIS, Access to treatment: unequal care for European rare disease patients, A Rare Barometer survey, February 2017.
- 27 PhRMA, The Biopharmaceutical Industry Profile, 2018; EFPIA, The Pharmaceutical Industry in Figure 2018.
- 28 Ibid.; JA DiMasi et al (2003). "The price of innovation: new estimates of drug development costs." *Journal of health economics* 22.2 (2003): 151-185.
- 29 See: Pugatch Consilium (2014). Scaling Global Clinical Trial Activity: Key Trends and Policy Lessons, p. 16.
- 30 PhRMA, The Biopharmaceutical Industry Profile, 2013, p. 37.
- 31 See: Haque, A. et al. (2017). "Postmarketing Surveillance Studies—An Industry Perspective on Changing Global Requirements and Implications", *Clinical Therapeutics*, Vol. 39, Issue 4, pp. 675-685; Ridley, D. B. et al. (2006). "Spending on Postapproval Drug Safety", *Health Affairs*, Vol. 25, No. 2; IgeaHub, Evaluation of Clinical Trial Costs and Barriers to Drug Development, clinical research, Perspectives, 28.8.2018, <https://www.igeahub.com/2018/08/28/evaluation-of-clinical-trial-costs-and-barriers-to-drug-development/>.
- 32 Deloitte, Measuring the return from pharmaceutical innovation 2017: A new future for R&D?, <https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/measuring-return-from-pharmaceutical-innovation.html>.
- 33 PhRMA (2013), 2013 Biopharmaceutical Research Industry Profile.
- 34 Paul, S. M. et al. (2010), "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge", *Nature Reviews Drug Discovery*, Vol. 9, pp. 2013-214.
- 35 Tufts Center for the Study of Drug Development (2018). Patent-to-launch time for orphan drugs is 2.3 years longer vs. other drugs, *Impact Report*, Vol. 20, No. 3, May/June 2018.
- 36 Ibid.
- 37 See for example: Gliklich, R.E., Dreyer, N.A., Leavy, M.B. (Eds). *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd Ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 20, Rare Disease Registries.

- ³⁸ See: Huml, R. A. and Dean, M. (2017). Designing Effective Rare Disease Registries, *R&D Mag*, 12.4.2017, <https://www.rdmag.com/article/2017/04/designing-effective-rare-disease-registries>; Joseph, A. Drug developers fund patient registries to collect data on rare diseases, *Statnews*, 16.12.2015, <https://www.statnews.com/2015/12/16/17473/>; EURORDIS, Rare Disease Patient Registries, Policy Fact Sheet, 2013, https://www.eurordis.org/sites/default/files/publications/Factsheet_registries.pdf; Gliklich, R.E., Dreyer, N.A., Leavy, M.B. (Eds). *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd Ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 20, Rare Disease Registries.
- ³⁹ Article 1 of the Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 018, 22/01/2000.
- ⁴⁰ European Medicines Agency, Orphan Designation, <https://www.ema.europa.eu/en/glossary/orphan-designation>.
- ⁴¹ European Commission (2016). Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products – State of Play 2015, SWD(2015)13 Final, https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_inv_report_20160126.pdf (accessed November 2018).
- ⁴² Jenkins (2013), "Developing Orphan Drugs in Europe", Patent Issues Jenkins Information Sheet 02/2013, http://www.maucherjenkins.com/assets/Publications/Fact%20Cards%20and%20Guides/Orphan%20Drugs_aligned-3.pdf
- ⁴³ EMA website, "Marketing Authorisation and Market Exclusivity" (accessed March 2017), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/_content_000392.jsp&mid=WC0b01ac058061f019
- ⁴⁴ Sumin Kim (2013), "The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity", *North western Journal of Technology and Intellectual Property*, Issue 11, Vol.6, Art.3, <http://scholarlycommons.law.northwestern.edu/cgi/viewcontent.cgi?article=1200&context=njtip>
- ⁴⁵ See for example the European Public Assessment Reports on Lenalidomide, Bortezomib, Temezolomide and miglustat, at: European Medicines Agency, Medicines, <https://www.ema.europa.eu/en/medicines>.
- ⁴⁶ Article 9 of the Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 018, 22/01/2000.
- ⁴⁷ Article 12(4)(b) and (c) of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare and the European Commission Implementing Decision of 10 March 2014 setting out criteria for establishing and evaluating European Reference Networks and their Members and for facilitating the exchange of information and expertise on establishing and evaluating such Networks (2014/287/EU), OJ L 147/79, 17.5.2014.
- ⁴⁸ EURORDOS, Centres of Expertise, 2013 EURORDIS Policy Fact Sheet, https://www.eurordis.org/sites/default/files/publications/factsheet_Centres_Expertise.pdf.
- ⁴⁹ See: E-Rare, The Project, <http://www.erare.eu/project>.
- ⁵⁰ See: European Commission, Research & Innovation, Rare Diseases, Commission activities in the area of Rare diseases, <http://ec.europa.eu/research/health/index.cfm?pg=area&areaname=rare>.
- ⁵¹ At the time of research the process is still in the proposal submission stage. See: European Commission, Call for Proposals for Project Rare Diseases - Support for New Registries Approved Erns (European Reference Networks), http://ec.europa.eu/research/participants/data/ref/other_eu_prog/hp/hp_call_proposals_pj-ern-rd-reg-2016_en.pdf (accessed October 2018).
- ⁵² Todd Gammie & Christine Lu (2015), "Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries", 10/9/2015, <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140002>.
- ⁵³ Hiroshi Takeda/MHLW (2014), "Incentives and Regulatory Considerations in Orphan Drug/Medical Device Development Situation in Japan", http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/03/WC500164166.pdf; Vishva V. Ramlall (2004), "The Pharmaceutical Industry in The Great White North and Land of the Rising Sun: A Comparison of Regulatory Data Protection in Canada and Japan", https://www.iip.or.jp/e_e_summary/pdf/detail2003/e15_12.pdf
- ⁵⁴ Thomas Morel et al. (2016), "Regulatory Watch: The Orphan Drug Pipeline In Europe", June 2016, https://www.researchgate.net/publication/303717564_Regulatory_watch_The_orphan_drug_pipeline_in_Europe; Pauwels K, Huys I, Casteels M, Larsson K, Voltz C, Penttila K, Morel T and Simoens S (2017) "Are products with an orphan designation for oncology indications different from products for other rare indications? A retrospective analysis of European orphan designations granted between 2002-2012", *Orphanet Journal of Rare Diseases* 12:36. See also: European Commission, call for proposals to a study supporting the evaluation of the EU orphan legislation, 2018, Annex II – Technical Specifications, p. 7.
- ⁵⁵ Charles River Associates, An evaluation of the economic and societal impact of the orphan medicine regulation, November 2017, p. 27.
- ⁵⁶ Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J & Garau, M. (2017). Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. Office of Health Economics (OHE) Consulting Report.
- ⁵⁷ See: European Medicines Agency, Supporting orphan medicines development and addressing significant benefit requirements through protocol assistance, SME Info Day, 17.11.2017, Matthias Hofer, https://www.ema.europa.eu/documents/presentation/presentation-supporting-orphan-medicines-development-addressing-significant-benefit-requirements_en.pdf; Manabu Murakami & Mamoru Narukawa (2016), "Matched Analysis On Orphan Drug Designations And Approvals: Cross Regional Analysis In The United States, The European Union, And Japan", *Drug Discovery Today*, Volume 21, Issue 4, April 2016, Pages 544–549.
- ⁵⁸ Annual figures for orphan products available for paediatric populations are based on Orphanet lists of medicinal products for rare diseases in Europe of July 2018, and include only innovative products (i.e. no generic / biosimilar products) with an active European Community marketing authorisation under the centralised procedure, with or without a European orphan designation. Annual figures for orphan products available for adult populations only rely on the meeting report on the review of applications for orphan designation by the Committee for Orphan Medicinal Products (COMP), September 2018, Annex I.
- ⁵⁹ See: Orphanet's lists of medicinal products for rare diseases in Europe, July 2018, https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf (the number of orphan medicinal products treating children is based on the inclusion of 'paediatric' or 'children' in the indication authorised for marketing).
- ⁶⁰ EURORDIS (2007), "What Is A Rare Disease?", 4/17/2007, http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf; Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- ⁶¹ Austin, C. P. et al. (2017). "Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective", *Journal of Clinical and Translational Science*, Vol. 11, Issue 1, pp. 21–27.
- ⁶² Global Genes, Rare diseases: Facts and Statistics, <https://globalgenes.org/rare-diseases-facts-statistics/>.
- ⁶³ See for example: The Academy of Medical Sciences, Academia, Industry and the NHS: Collaboration and Innovation, FORUM Meeting Report, October 2010, <https://acmedsci.ac.uk/file-download/35209-Collabor.pdf>; Palmer, M & Chaguturu, R. (2017). "Academia-pharma partnerships for novel drug discovery: essential or nice to have?", *Expert Opinion on Drug Discovery*, Vol. 12, No. 6, pp. 537-540; Taylor, A. P. (2018). How to Successfully Collaborate with Industry, *The Scientist*, March 1, 2018, <https://www.the-scientist.com/careers/how-to-successfully-collaborate-with-industry-30012>.
- ⁶⁴ See: EMA, Human Regulatory, Adaptive Pathways, <https://www.ema.europa.eu/human-regulatory/research-development/adaptive-pathways>.
- ⁶⁵ Ibid.
- ⁶⁶ See: European Health Forum Gastein, Tackling uncertainties for rare diseases - The use of RWE to improve access for patients, <https://www.ehfg.org/conference/session-content/l6/>; European Health Forum Gastein, Tackling uncertainties for rare diseases (L6), <http://www.ehfg.org/blog/2018/10/05/tackling-uncertainties-for-rare-diseases-l6/>; a final consensus paper will be published during 2019.
- ⁶⁷ For a comprehensive discussion on the role of clinical research within the biopharmaceutical innovation process, and its social and economic benefits to hosting countries, see: Pugatch Consilium (2014). *Scaling Up Global Clinical Trial Activity: Key Trends and Policy Lessons*, www.pugatch-consilium.com
- ⁶⁸ Pugatch Consilium (2014). *Scaling Up Global Clinical Trial Activity: Key Trends and Policy Lessons*, pp. 14-18.

- ⁶⁹ There are several international clinical trial registries, including the World Health Organization's ICTRP and the EU Clinical Trial Register. Clinicaltrials.gov is recognized in the academic literature as the most reliable and encompassing registry (see for example: Knelangen, M. et al. (2017). "Trial registry searches for randomized controlled trials of new drugs required registry-specific adaptation to achieve adequate sensitivity", *Journal of Clinical Epidemiology*, Vol. 94, pp. 69-75; Viergever, R.F., Li, K. (2015). "Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013". *BMJ Open*, 5). Furthermore, clinicaltrials.gov also includes quality control over its data, as well as the option to download its entire content for analysis. For these reasons, the analysis of clinical trials on rare diseases relies on clinicaltrials.gov database. There are currently 1,913 rare medical conditions on which clinical trials are registered in clinicaltrials.gov. See: clinicaltrials.gov, Find studies by topic, Rare Diseases, https://clinicaltrials.gov/ct2/search/browse?brwse=ord_alpha_all.
- ⁷⁰ See: https://www.orpha.net/consor4.01/www/cgi-bin/Disease_Search_List.php?lng=EN.
- ⁷¹ The entire dataset of circa 50,000 clinical trials was reviewed for duplication, errors and mismatches; observational and expanded access trials were excluded (See: <https://clinicaltrials.gov/ct2/about-studies/glossary>).
- ⁷² The analysis includes clinical trials for which a rare condition is among the medical conditions registered.
- ⁷³ See: Julkowska, D. et al. (2017). "The importance of international collaboration for rare diseases research: a European perspective", *Nature: Gene Therapy*, Vol. 24, pp. 562-571; European Commission, Rare Diseases, https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en.
- ⁷⁴ Héon-Klin, V.(2017). "European Reference networks for rare diseases: what is the conceptual framework?", *Orphanet journal of rare diseases*, Vol. 12, Issue 1.
- ⁷⁵ Commission of the European Communities, Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained, p. 9, Brussels, 20.6.2006, https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_en_06-2006_en.pdf.
- ⁷⁶ Commission of the European Communities, Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained, p. 13, Brussels, 20.6.2006, https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/orphan_en_06-2006_en.pdf.
- ⁷⁷ Zamora et Al. (2017). Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries, Office of Health Economics.
- ⁷⁸ This is the average duration for England, Scotland, Wales, France, Germany, Italy and Spain. Germany is excluded as all products are reimbursed upon approval. When Germany is included, the average duration drops from 23.4 months to 20 months.
- ⁷⁹ See: EURORDIS, The EURORDIS Access Campaign, <https://www.eurordis.org/content/country-results-eurordis-access-campaign-patient-survey> (accessed October 2018).
- ⁸⁰ Ibid.
- ⁸¹ See: EURORDIS, Access to treatment: unequal care for European rare disease patients, A Rare Barometer survey, February 2017 (accessed: October 2018).
- ⁸² See: European Commission, Commission Staff Working Document, Impact Assessment, Strengthening of the EU Cooperation on Health Technology Assessment (HTA), Accompanying the document, Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU, <http://data.consilium.europa.eu/doc/document/ST-5844-2018-ADD-1/en/pdf> (accessed November 2018).
- ⁸³ Ibid., pp. 66-71.
- ⁸⁴ European Commission (2006) Commission staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained.
- ⁸⁵ Schey et al. Estimating the budget impact of orphan medicines in Europe: 2010 – 2020. *Orphanet Journal of Rare Diseases* 2011, Vol. 6, No. 62.



CONTACT US

UK Office

88 Sheep Street, Bicester, Oxon OX26 6LP
Tel: +44 1869 244414 Fax: +44 1869 320173

E: info@pugatch-consilium.com

FOLLOW US

For more information on our services, to read our research reports or media coverage and for all the latest Pugatch Consilium news, please take a look at our online news room and blog or follow us on social media.

www.pugatch-consilium.com

[Twitter@PConsilium](https://twitter.com/PConsilium)

