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COMMISSION STAFF WORKING DOCUMENT

EVALUATION

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

{SEC(2020) 291 final} - {SWD(2020) 164 final}

ANNEX 4: COSTS AND BENEFITS

This Annex provides a table giving an overview of all costs and benefits.

OVERVIEW OF COSTS AND BENEFITS OF THE ORPHAN REGULATION							
		Citizens/Consumers		Businesses		Administrations	
		Qualitative	Quantitative / monetary	Qualitative	Quantitative / monetary	Qualitative	Quantitative / monetary
Aid for research	**Economic cost** for EU and various national governments, which provided subsides to stimulate the development of orphan medicines. **Directly** related to the rewards of the Orphan Regulation					With the very limited information available, it was not possible to assess the extent to which these additional R&D expenditures would have been incurred without the Orphan Regulation.	These costs have been estimated at -/- **€1.1b**
Fee waiver, protocol assistance	**Economic cost** for administration (EMA) **Economic benefit** for businesses			Interviewees from industry have suggested that protocol assistance is most valuable to relatively inexperienced developers. In general, developers of products for which demonstration of	The value of those rewards can be expressed in monetary terms. The value of the provision of the fee waiver and protocol assistance rewards under the EU Orphan Regulation during 2000-2017 is estimated at **€0.16b** (discounted value 2018).		The costs of this assistance, which are incurred by the EMA, are fully financed by the EU and have been estimated at **-/- €0.2b**

				significant benefit is required stand to benefit from protocol assistance. The importance of fee reductions is higher for SMEs (for which fees can be waived completely) than for large pharmaceutical companies for whom such fees are a relatively minor cost			
Administration: EMA/COMP costs	Additional **economic cost** resulting from the tasks that EMA executes in relation to the EU Orphan Regulation, as well as the cost borne by the EEA member states and other					Member States contribute indirectly by nominating national experts as members to the COMP. These members are not reimbursed for their work in the COMP. The organisations from which they are seconded thus indirectly bear the costs as a result of time	Annual costs for EMA and national governments have been assessed based on the approximate number of staff (in full time equivalents) involved in the various activities relating to the EU Orphan Regulation. **-/- €0.02b**

	organisations in relation to the meetings of the various committees discussing applications for orphan designations and marketing authorisations. **Directly** related to the rewards of the Orphan Regulation					spent by COMP members outside these institutions. No estimates are available of these costs.	
R&D costs for new orphan medicines	**Economic cost** for businesses			Companies were reluctant to provide information on absolute expenditure on R&D on orphan medicines. An attempt was made to gain insight into the *relative* costs of development of	As the results from the consultations did not provide a sufficiently robust input for our analysis, the study used estimates of R&D costs for orphan medicines found in literature. Using the above estimates and assumptions, the EU Orphan Regulation is estimated to have led to an increase of **€11.0b**		

				orphan medicines (compared to non-orphans). However, such information could not be used in any meaningful way (few and different answers). As the results from the consultations did not provide a sufficiently robust input for our analysis, the study used estimates of R&D costs for orphan medicines found in literature.	(discounted value 2018) in R&D expenditure for orphan medicines in the period 2000-2017.		
Extra costs for manufacturing, marketing, distribution orphan medicine	**Economic cost** for businesses				The assessment of these costs was based on the methodology used to assess the economic value of the market exclusivity reward. Based on the extra sales of €19.1b (see below), these costs over the years 2000-2017 were		

					assessed at **€12.04b** (discounted value 2018) after deducting from the extra sales benefits to the industry related to an exclusivity margin (30%) and a competitive profit margin (10%); the latter assumed to be a margin that would (continue) to apply even when generic price competition occurs and hence already applies as a benefit during market exclusivity.		
Private contribution to health care costs[1]			**-/- €0.7b** The private contribution by patients is assessed at 3% of additional health care costs.				

[1] In the analysis it was assumed that, in the EU, the large majority (97%) of all health care costs that are directly due to treatment with orphan medicines (excluding associated costs of treatment) is financed from public sources.

Change in non-health costs of disease			NDA				
Additional impact on health costs			NDA				NDA
Extra health care costs financing	**Economic costs** for the (national) health system. These are the costs related to providing medicines to patients living with rare diseases.					Direct impacts on health care costs are typically taken into account in Health Technology Assessment (HTA). HTA reports were identified for 32 orphan medicines that contain information on ICERs, but only a few of them disclose the additional underpinning information. As a result, the impact on additional costs of treatment with orphan medicines or cost-savings in the health care system could not be assessed.	The extra costs for the health care system have been assumed to be equal to the extra revenues realised by industry (sales revenues and revenues deriving from market exclusivity19,1b + 4,6b). **-/- €23.7b**
Costs relating to financing of	**Economic cost** for health sector					A large part of the additional health care	For the analysis a 97%-3% division has been

extra costs of the health sector						costs is reimbursed from collective sources (either government budgets, collective health insurance systems or otherwise). Healthcare systems across the EU Member States are organised and financed in different ways. Surveys with representatives of national authorities provided some relevant information. Based on this information, only a small proportion of costs related to orphan medicines was considered to be financed from out-of-pocket expenses by patients, most likely less than 5% of the total	used between public and private financing. Health care financing costs were estimated at -/- **€23.0b**
Extra sales revenues	**Economic benefit** for businesses				The estimated value of increased sales of orphan medicines in the EU market in 2000-2017 of an estimated value of **€19,11**		

					b (discounted value). Almost 45% of this is due to sales from newly developed orphan medicines, another 44% is due to faster access to EU/EAA market of the other 110 orphan medicines and 11% due to wider spread of medicines.		
Revenues from market exclusivity reward	**Economic benefit** for businesses			In the survey to developers, the market exclusivity reward was identified as the most important incentive of the EU Orphan Regulation, with 95% considering it 'important' or, most often, 'very important'.	As the additional R&D compensation offered by market exclusivity may co-exist with (multiple) other forms of protection (for instance, when the market exclusivity period overlaps with the patent/SPC protection), its value could not be quantified. Only the impact of the longer duration of the protection could be taken into account. On average, the additional protection period resulting from the market exclusivity was 3.4		

					years. The estimated value of this extra R&D compensation was **€4.59b.**		
Revenues for the health system	**Economic benefit for (national) health system**						The extra costs for the health systems resulting from the EU Orphan Regulation need to be recovered from public and private sources. It has been assumed in the analysis that such costs are fully covered, implying that costs and benefits for the health system are balanced. Effectively, this means that the cost estimates provided here are carried over to another set of stakeholders, including governments (in case of publicly funded health systems) and patients (e.g. through insurance premiums and when co-payments apply). **€23,7b**

Health benefits	Benefits concern the **improvement in the quality of life of patients** due to the treatment with orphan medicines. These benefits can be expressed in terms of the number of quality-adjusted life years (QALY)[2] gained by patients.	The level of health benefits has been assessed using information on the Incremental Cost-Effectiveness Ratio (ICER[3]), from HTA reports.	Based on a multiplication of the calculated ICERs (range €54,000 to €110,000) and the estimated extra health care costs presented above, it is estimated that, as a result of the Regulation, **210,000 to 440,000 QALYs were gained**.				

[2] A QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance. (https://www.nice.org.uk/glossary?letter=q). For more information about QALY, see for instance: MacKillop & Sheard, 2018, Quantifying life: Understanding the history of Quality-Adjusted Life-Years (QALYs), Social Science and Medicine, volume 211.

[3] The incremental cost-effectiveness ratio is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest. (https://www.nice.org.uk/Glossary?letter=I) It is therefore a measure for the 'value for money' a medicine offers in comparison to other treatments.

NET benefits			-/- €0.7b		+€0.82b		-/- €24.3b
ICER			€54,000 to €110,000				
Net societal cost per QALY			€58,000 to €118,000				

NDA: No data available to assess this impact

OVERVIEW OF COSTS AND BENEFITS OF THE PAEDIATRIC REGULATION							
		Citizens/Consumers		Businesses		Administrations	
		Qualitative	Quantitative / monetary	Qualitative	Quantitative / monetary	Qualitative	Quantitative / monetary
Costs for compliance with the Regulation - Research	**Economic cost** for businesses to conduct paediatric clinical research mandated by the Regulation **Directly** related to the Paediatric Regulation			The costs incurred by individual PIPs vary significantly depending by the type of clinical trials to be conducted, the number of subjects involved and the therapeutic area concerned	These costs have been estimated at **€2,0 b** per year. The estimated average cost of each PIP is of **€18,9 m (**cost incurred over several years).		
Costs for compliance with the Regulation – Administrative costs	**Economic cost** Administrative costs for businesses to comply with the Regulation				The costs are related to the filing of a PIP applications and are estimated at **€82 m** per year.		

	Directly related to the Paediatric Regulation						
Costs Administration: remuneration of the work of national competent authorities	Costs for the remuneration of the National competent authorities for their work on PIP related procedures **Directly** related to the Paediatric Regulation					Costs estimated on the basis of unpublished data collected in the framework of the evaluation of the EMA fees system.	Estimated annual costs for NCAs for PIP related procedures: PIP assessments: **€ 0,6 m** PIP waivers **€ 90.000** PIP compliance checks **€50.000**
Costs for society linked to the marketing of paediatric medicinal products	**Economic cost** society due to the monopoly rent (linked to the SPC extension) and revenues of other beneficiaries (like wholesalers		Estimated cost **€ 590 m** over a 10 year period (€ 551 m are estimated to be direct costs to the national health services.				

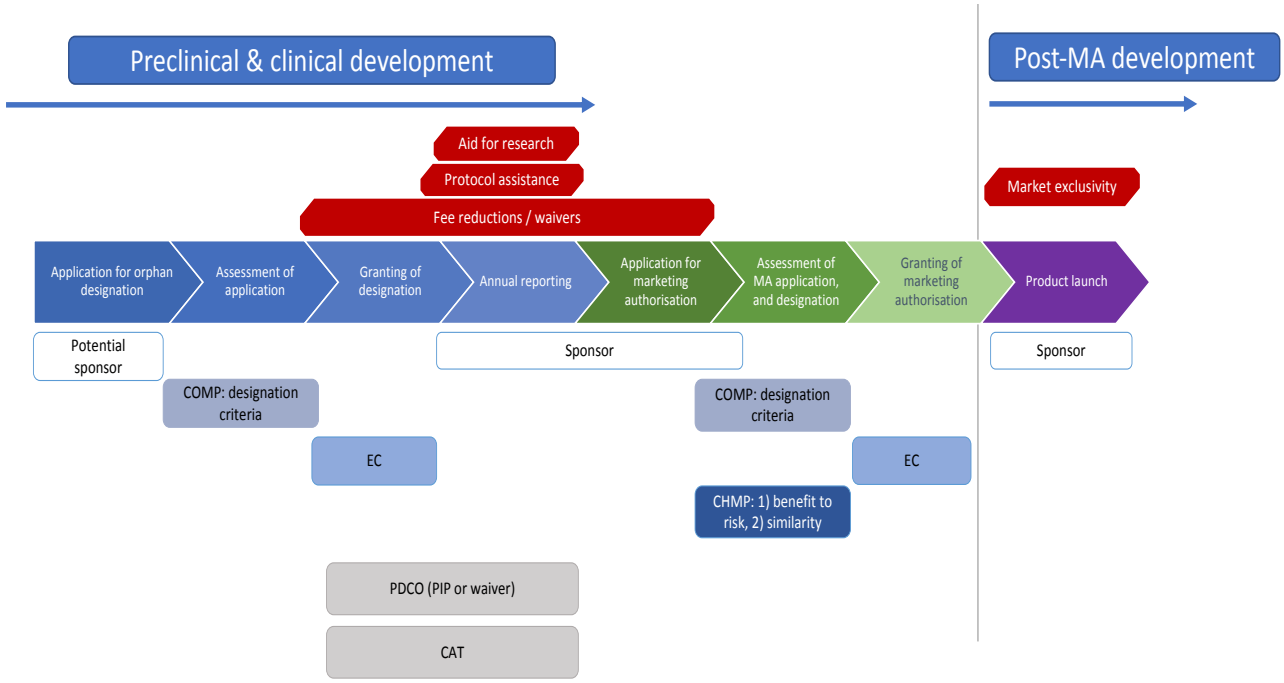
	Directly related to the rewards of the Paediatric Regulation						
Benefit **To society due to cash and non cash benefits following the marketing of new paediatric medicines**	**Economic benefit** These include: -cash benefit linked to avoided adverse reactions due to the use of medicines untested in children (avoided hospital stays and outpatients visits) - Non cash benefits for which monetary benefit has been calculated: improved	2 estimates have been calculated, one on the basis of real data of 8 products which have obtained an SPC extension and have already lost their exclusivity (estimate 1) and a second estimate of future benefits for a larger basket of products but for which data needed to be extrapolated, This basket includes products which may not receive an SPC extension (estimate 2).	Estimate 1: € 199 m over a 10 years period Estimate 2: € 500 m over a 10 years period				

	treatments for children, reduced mortality, improved quality of life, avoided long-term disabilities, time saved by informal carers						
Benefit **For businesses due to the monopoly rent**	**Economic benefit** for businesses due to the monopoly rent linked to the SPC extension **Directly** related to the Paediatric Regulation			The estimate has been calculated, one on the basis of real data of 8 products which have obtained an SPC extension and have already lost their exclusivity.	This benefit is estimated in **€ 520 m**		
Benefits for businesses due to the obtention of	**Economic benefit** for businesses			Only a limited number of orphan rewards and PUMA have been	NDA		

ten orphan rewards or for the use of the PUMA procedure				granted. There are therefore insufficient data to assess their economic value			
Benefit **Spill over effect for society due to investments in R&D by businesses linked to the Paediatric regulation**	**Economic benefit** for society Jobs creation, promotion of innovation linked to the R&D investments by businesses linked to the Paediatric Regulation	The estimation is calculated as a result of an investment of € 2 b. in R&D by businesses following the obligations of the Paediatric Regulation	Estimated in **€6 b**. over 10 years				
Benefit **Intra industry and cross industry spill over effect due to investments in R&D by businesses**	**Economic benefit** for businesses intra sector and cross-sector jobs creation, promotion of innovation linked to the			The estimation is calculated as a result of an investment of € 2 b. in R&D by businesses following the obligations of the Paediatric	Estimated in **€3,2 b**. over 10 years		

linked to the Paediatric regulation	R&D investments by businesses linked to the Paediatric Regulation			Regulation			

ANNEX 5: AGENCY'S COMMITTEES



COMP = Committee for Orphan Medicinal Products; **PDCO** = Paediatric Committee; **PIP** = Paediatric Investigation Plan; **CAT** = Committee for Advanced Therapies; **CHMP** = Committee for Medicinal Products for Human Use; **MA** = Marketing Authorisation.

Source: Orphan study report (2019)

Committee for Orphan Medicinal Products (COMP)

COMP is involved in the implementation of the EU Orphan Regulation. It meets every month to discuss applications to assess their eligibility against all applicable criteria (e.g. prevalence, medical plausibility, significant benefit), to determine the orphan indication, to adopt opinions and prepare summary reports, which are then sent to the European Commission. These meetings currently take around three days each time.

Whereas it is at the discretion of the Member States to decide who they would like to nominate, the COMP internally seeks for a good balance of expertise by having members who represent different clinical fields and backgrounds. Many hold positions in national ministries or national competent authorities, whereas others hold positions in academia or clinical practice. However, all members are nominated on a personal title.

Committee for Medicinal Products for Human Use (CHMP)

All products for which a marketing authorisation is sought through the centralised procedure must be assessed by the Committee for Medicinal Products for Human Use (CHMP), regardless of whether they have an orphan designation. The CHMP will conduct a scientific assessment to establish the benefit to risk ratio of the product, and thus determine whether the product should be allowed onto the European market and, if so, for which therapeutic indication(s).

The purpose of the scientific assessment performed by the CHMP is thus a different one from that conducted by the COMP, which focuses on the fulfilment of the criteria for orphan designation.

The CHMP is also responsible for assessing similarity for applications for marketing authorisation for products with an orphan designation in case there is already an authorised product on the market for the same orphan indication that is still protected by market exclusivity.

Paediatric Committee (PDCO)

Since the introduction of the Paediatric Regulation in 2007, developers should submit a 'Paediatric Investigation Plan (PIP) for all products "not later than upon completion of the human pharmacokinetic studies".[4]

Only when there is sufficient justification that paediatric investigations are not warranted, such as when the product targets a condition that does not affect children, can the obligation to submit a PIP be waived. In case of compliance with an agreed PIP, a marketing authorisation holder is eligible for the so-called 'paediatric extension', a 6-month extension of the Supplementary Protection Certificate (SPC). In the case of designated orphan medicines, however, a different reward is offered in the form of an additional two years of orphan market exclusivity.

All PIPs are assessed by the Paediatric Committee (PDCO), including in the case of designated orphan medicines. The Paediatric Regulation and the Orphan Regulation intersect at the point where products are being developed for the treatment of rare diseases that occur in children. In such cases, both the COMP and the PDCO have roles to play in the regulatory assessment process.

To increase cooperation across regions, a discussion forum to regularly exchange information mainly via teleconferences ('paediatric cluster') was formed in 2007, including members of the US FDA and the Agency (PDCO). The cluster has since been joined by the Pharmaceuticals and Medical Devices Agency (PMDA) Japan, Health Canada, and the Australian Therapeutic Goods Administration (TGA) as an observer. In 2013 the Agency and its US counterpart launched so-called 'common commentaries' on paediatric development plans that have been submitted to both the Agency and FDA and that are therefore being reviewed by both agencies. While informal and non-binding, these commentaries and

[4] Section 5.2.3 of Part 1 of Annex 1 of Directive 2001/83/EC).

discussions between the two agencies have helped to align views and to avoid contradictory requirements on the paediatric development programme.

Committee for Advanced Therapies (CAT)

An increasing share of orphan medicines fall into the category of 'advanced therapy medicinal products' (ATMPs). In 2007, the new EU Regulation for ATMPs, Regulation (EC) No 1394/2007, was introduced which "lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products" (Article 1).

Along with the introduction of the Regulation, the Committee for Advanced Therapies (CAT) was established, which is responsible for conducting the assessment of whether a product meets the criteria for designation as an ATMP.

Like the orphan designation, designation as an ATMP is optional. The ATMP Regulation offers a set of incentives to developers of ATMPs. These incentives are all linked to the Agency's services and procedures.

Unlike the Orphan Regulation and the Paediatric Regulation, the ATMP Regulation does not provide any incentives in the form of extended market exclusivity rights. The incentives conferred by the ATMP classification are cumulative to those that come with the orphan designation.

ANNEX 6: IMPLEMENTATION OF THE VARIOUS INCENTIVES

Incentives (Regulation)

Market exclusivity

This exclusivity means that a regulatory competent authority cannot authorise the same or a 'similar' medicine for the same orphan indication, nor can it take an application for authorisation into consideration whilst an exclusivity period is in effect on a first product, even when that product is not protected by a patent.[5]

It can be extended by two more years if the application for a marketing authorisation includes the results of all studies conducted in compliance with an agreed Paediatric Investigation Plan (PIP).[6]

Market exclusivity for orphan medicines is cumulative with patents/supplementary protection certificates and with existing regulatory frameworks for data exclusivity and market protection.[7]

Market exclusivity period may be reduced to six years if:

- "at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable

[5] Article 8 of Regulation 141/2000 states: 'Where a marketing authorisation in respect of an orphan medicinal product is granted (…) or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition (…) the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.' A marketing authorisation for a product similar to one under market exclusivity can only be granted if one of the derogation options under Article 8(3) of Regulation (EC) No 141/2000 applies.

[6] See article 37 of Regulation No 1901/2006 on the Regulation on medicinal products for paediatric use.

[7] Data exclusivity is a form of protection conferred on the dossier of trial results that the marketing authorisation holder submitted to obtain approval. The exclusivity means that for a period of 8 years, a company that seeks to produce a generic version of the product cannot reference the data. The scope of protection thus differs from the market exclusivity in that the protection is on the *data* rather than on the *product*.
After the 8-year data exclusivity, the marketing authorisation holder still is entitled to a 2-year period of market protection during which it has the sole right to market the product. One additional year of market protection (represented by '+1') can be granted in the case of:
1. Additional therapeutic indications with significant therapeutic value,
2. New indications for well-established substances, or
3. When new data is submitted to support a change in classification.

During the period in between the expiry of data exclusivity and that of market protection, third parties can file for a marketing authorisation by referring to the data of the reference product but cannot yet bring the product on the market. This differs from the orphan market exclusivity, during which the Agency will not yet consider any such applications. Together, the scope of protection from data exclusivity and market protection also differs from that of market exclusivity in that all subsequent variations of the product or any additional indications cannot trigger a new period of protection, as these would come under the same Global Marketing Authorisation.

not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and th4e Agency shall then initiate the procedure laid down in Article 5.

Protocol assistance

While the market exclusivity reward can be seen as the major incentive for the development and marketing of orphan medicines, particularly for the eventual marketing authorisation holder, the EU Orphan Regulation also foresees in the provision of a specific form of scientific advice by the Agency, known as 'protocol assistance' for orphan medicine developers (Article 6).[8] This implies that, in addition to the general scientific advice the Agency can provide on appropriate tests and studies in the development of a medicine, orphan medicine developers can seek advice in relation to the criteria for authorisation of orphan medicines.

Fee waivers

If sponsors obtain a marketing authorisation or make use of other services of the Agency, they normally have to pay certain fees (European Medicines Agency, 2017c). Various main fee categories can herein be distinguished, including:

- Centralised procedure, covering fees for the application, extension and variations to a marketing authorisation;
- Scientific advice;
- Scientific services.

The system contains various exemptions, such as fee reductions for small or medium-sized enterprises (SMEs), some fee reductions in case of multiple applications on usage patent grounds, as well as fee reductions for designated orphan medicines. The latter is funded by a special annual contribution to the Agency (Article 7 sub 2).

Table A.32: Fee reduction for designation orphan medicines

Procedure or service	Applicable to	Reduction
Protocol assistance, initial and follow-up requests	SME sponsors for all assistance	100%

[8] Article 6 of Regulation 141/2000 states: "The sponsor of an orphan medicine may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product (…)".

	Non-SME sponsors for non-paediatric-related assistance	75%
	Non-SME sponsors for paediatric-related assistance	100%
Pre-authorisation inspection	All sponsors	100%
Initial marketing authorisation application	SME sponsors	100%
	Non-SME sponsors	10%
Post-authorisation applications and annual fee, specified in Council Regulation (EC) No 297/95, in the first year from granting of a marketing authorisation	SME sponsors	100%
Pharmacovigilance fees, specified in Regulation (EU) 658/2014	All sponsors	n/a

Source: Orphan study report (2019)

Aid for research

Besides the market exclusivity reward, the protocol assistance and the fee waiver, the EU Orphan Regulation introduced the incentive 'aid for research' (Article 9).[9] This incentive makes it possible for the European Commission and/or Member States to provide additional funding for the research and development of designated products. The self-evident intent of this incentive is to further encourage investments in, in particular, the early stages of research into rare diseases. Such basic research is important to elucidate the mechanisms underpinning rare diseases, which in turn is a prerequisite for product development.

What these European and national programmes together demonstrate is that, overall, in the 18 years since the introduction of the EU Orphan Regulation, there has been a clear increase in research-related accompanying measures, and specifically in the:

- Level of public funding available for rare disease research, at the EU and national levels;
- Level of coordination of national and international research agendas in rare diseases;

[9] Article 9 of Regulation 141/2000 states: 'Medicinal products designated as orphan medicines under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicines and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.'

- Extent of the data and knowledge infrastructure for rare diseases, from patient registries to biobanks.

EU research and innovation programmes

EU Framework Programmes

The EU's support for rare disease research was initiated within the fourth EU RTD Framework Programme (FP4) and confirmed and expanded within the fifth Framework Programme (FP5), with the number of supported projects increasing from 23 within FP4 to 47 within FP5.

In the intervening period and following the implementation of the EU Orphan Regulation in 2000, the EU reconfirmed its commitment to rare disease research with a larger programme of work within each successive EU RTD Framework Programme.

Since 2000 for more than two decades, rare disease research has been a priority for the EU.[10] More specifically, the sixth Framework Programme for research and technological development (2002-2006) (FP6) supported 59 projects with approximately €230 m. The seventh Framework Programme[11] for research, technological development and demonstration activities (2007-2013) (FP7) supported more than 120 rare disease projects under the *Health* theme with approximately €620 m. Support was available for projects that shed light on the course and/or mechanisms of rare diseases, or test diagnostic, preventive or therapeutic approaches.[12]

Horizon 2020[13] has continued the EU's commitment to funding rare disease research and upon its completion will likely have more than doubled the investment made under FP7. In its 2017 publication,[14] the European Commission indicated that, in 164 collaborative research projects into rare diseases had been supported until that time by FP7 and H2020, with a total value of €874m out of which SMEs were supported with €180m. Horizon 2020 and FP7 combined have committed more than €1b to collaborative rare disease research over the last ten years.

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10 https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/p4p_en

11 https://wayback.archive-it.org/12090/20191127213419/https:/ec.europa.eu/research/fp7/index_en.cfm

12 European Commission (2016), Working document: Ex-Post Evaluation of the Seventh Framework Programme, January 2016.

13 http://ec.europa.eu/research/participants/data/ref/h2020/wp/2018-2020/main/h2020-wp1820-health_en.pdf

14 https://op.europa.eu/en/publication-detail/-/publication/c2ba4fd4-ae31-11e7-837e-01aa75ed71a1/language-en/format-PDF/source-69927191

ERA-Net research programmes on rare diseases

The ERA-Net research programmes on rare disease research (E-Rare)[15,16] are a good example of the evolution of the Members States coordinated efforts in support to rare disease research in the 19 years following the implementation of the EU Orphan Regulation.

E-Rare was implemented first in 2006, in the closing stages of the sixth European RTD Framework Programme (FP6) with the aim of fostering an increased focus on rare disease research at the level of individual EU member states.[17] The pooled national funds were matched by EC funds and were used to support various coordination activities (e.g. setting of a common research agenda) and to fund transnational research to complement the bigger multinational groups funded by the EU.

The initial partnership, E-Rare 1, consisted of eight countries who issued two transnational calls in 2007 and 2009. The Commission approved a follow-on project under FP7 (E-Rare 2), which ran from 2010-2014. E-Rare 2 had an expanded network, with the original eight EU member states increasing to 15 countries and with annual calls for proposals. In addition to an increase in the number of research projects supported, the network also redoubled its efforts to enhance coordination among member states by enabling information exchange and extension of the rare disease research funders' network.

The network earlier success led to a further proposal within Horizon 2020 and the launch of E-Rare 3, again with a larger membership and an expanded agenda. E-Rare 3 is made up of 25 public bodies, ministries and research funding organisations from 17 countries.[18] Since its inception, E-Rare has launched eight Joint Transnational Calls (JTCs) for projects, with a total investment value of €92m.

The E-Rare network has established good links with the international rare diseases research community and its programme of work follows the basic guidelines defined by the International Rare Disease Research Consortium (IRDiRC).

International Rare Disease Research Consortium

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15 http://www.erare.eu

16 Julkowska D et al. The importance of international collaboration for rare diseases research: a European perspective. Gene Ther. 2017:24(9):562-57

17 The ERA-NET instrument is a generic instrument that provides EC financial support to Member State level 'public-public' partnerships (typically amongst research funders) in the preparation and implementation of joint research actions of a transnational nature.

18 Austria, Belgium, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Spain, the Netherlands, Switzerland, Israel, Turkey, Canada and Japan.

The European Commission has been actively driving international research collaboration in rare diseases. IRDiRC was established in 2011 by the European Commission (DG RTD) together with the US National Institutes of Health (NIH) and aims to strengthen rare disease research by coordinating rare disease research funding[19] at the global level. IRDiRC is a model of international research policy collaboration that brings together 59 organisations funding rare diseases research, patient advocates and industry, across five continents.[20]The IRDiRC recognises that coordinating efforts to overcome common barriers in the development of orphan medicines is key to maximising the impact of collective global investments. IRDiRC's Therapies Scientific Committee launched recently the Orphan Drug Development Guidebook[21], which aims at facilitating medicines development for rare diseases by organizing available tools in USA, Europe and Japan into a standardized framework.

Capitalizing on the momentum of this progress, IRDiRC devised its goals for the decade 2017-2027, to:

- enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention
- catalyse the approval of 1000 new therapies for rare diseases, the majority of which will focus on diseases without approved options.

RD-ACTION

The RD-ACTION[22] (2015-2018) project was set up to meet diverse challenges of rare diseases at EU level: it must expand and consolidate the achievements of two previous Joint Actions on Rare Diseases supported by the European Commission: Orphanet and the European Union Committee of Experts on Rare Diseases[23] (EUCERD) Joint Action.

European Reference Networks

[19] http://www.irdirc.org/

[20] 26 EU Member States (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, Spain, The Netherlands); 7 associated (Armenia, Georgia, Israel, Norway, Serbia, Switzerland, Turkey), UK and Canada.

[21] https://irdirc.org/activities/task-forces/orphan-drug-development-guidebook-task-force/

[22] http://www.rd-action.eu/

[23] The mandate of the EUCERD expired in 2014. The EUCERD has been succeeded by the European Commission Expert Group on Rare Diseases.

A European initiative to support both patient care and research on rare diseases is the creation of European Reference Networks (ERNs).[24] The ERNs primarily focus on the provision of advice, via an IT tool, on concrete patient's cases (for diagnosis and treatment) but also serve as information, research and knowledge centres with the aim of contributing to the most recent scientific findings.

Research is a key element of the ERNs, providing an integrated structure to facilitate collaboration and creating a knowledge hub to encourage translational research and the creation of cross-border registries. In March 2017, the first 24 ERNs were launched.

EU contributions to rare disease research

The EU has invested considerably in research for rare disease in other ways. This includes for instance support for basic research, such as what is supported through the EU framework programmes and support for the creation of an infrastructure to promote knowledge sharing. Estimates of the financial contributions so far have been summarised in Table A.12.

Table A.33: EC funding contributions to rare disease research

Initiative	**EC contribution to rare disease research**
Seventh Framework Programme for Research and Innovation (FP7)	€624m (based on non-public data provided by DG RTD extracted from the Cordis database)
Horizon 2020 and ERA-NETs (E-Rare 1, 2 and 3)	Contribution of €180-185m by the EC (€5m to E-Rare 1 and E-Rare2, nearly €120 m for new therapies for rare diseases , €5m for integration and opening research infrastructures and €55m for the Rare Disease European Joint Programme Cofund) In E-Rare 1 (2006-2010), and E-Rare 2 (2010-2014) overall €56.4m was invested. (Aymé S, 2013) In E-rare 3 (2015-2019), more than €90m was invested. (European Commission, 2017b)

[24] The ERNs were established in 2017: https://ec.europa.eu/health/ern_en

RD-ACTION (‘joint action’ on rare diseases)	€8.3m. (Hedley et al., 2016).
European Reference Networks	The ERNs are supported from several EU funding programmes, including the Health Programme, the Connecting Europe Facility and Horizon 2020.

Source: Orphan report (2019)

National research activities

At the level of the EU Member States, various ‘other incentives’ have been put in place to complement the EU Orphan Regulation and further support the development of orphan medicinal products.

A prominent place herein is taken by national rare disease plans. Such national rare disease plans are aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems. They commonly include a commitment to research funding.

It is, however, not known to what extent commitments have been converted into actual spending on research for rare diseases and development of orphan medicines.[25]

THE RESEARCH AND COORDINATION ASPECTS OF THE NATIONAL PLANS ANALYSED REVEALED A REASONABLY CONSISTENT PICTURE. A MAJORITY OF MEMBER STATES HAVE (OR HAD) A NATIONAL PROGRAMME FOR RARE DISEASE RESEARCH. IN MOST CASES, THERE ARE SPECIFIC RARE DISEASE PROGRAMMES. IN A MINORITY OF CASES, SUPPORT IS AVAILABLE THROUGH A BROADER MEDICAL RESEARCH PROGRAMME WHERE RARE DISEASE RESEARCH PROPOSALS WILL HAVE TO WIN GRANT FUNDING IN COMPETITION WITH

[25] Publications on existing programmes and their impact do not always make a distinction between (fundamental) research in the field of rare disease and the development of orphan medicines.

ANNEX 7: INTERNATIONAL CONTEXT

Comparison of criteria for orphan designation in the EU, US and Japan

	EU	US	Japan
Orphan condition	< 5 in 10,000 in EEA; OR without incentives it is unlikely that the marketing would generate sufficient return to justify the investment.	≤ 6 in 10,000 in US; OR an orphan subset of a non-rare disease; condition where the characteristics of the medicinal product limit its use in a particular subgroup; OR there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the US market and the costs of making the drug available in the US.	< 4 in 10,000 in Japan;
Medical need	No satisfactory methods of treatment (or prevention or diagnosis) for life-threatening or chronically debilitating condition exist; OR if any such methods exist the medicinal product must be of significant benefit to those affected by the condition, i.e.: a. conferring a clinically relevant advantage; OR b. a major contribution to patient care.	Not a criterion unless the same drug has previously been approved for the same use or indication, clinical superiority needs to be proven as follows: Shown to provide a significant therapeutic advantage over an approved drug in one or more of the following ways: (i) Greater effectiveness; (ii) Greater safety in a substantial portion of the target populations; (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.	No appropriate alternative drug/medical device treatment for serious disease including difficult to treat the disease; OR higher efficacy or safety is expected compared with existing products.
Medical plausibility/ scientific rationale	Usually *in vivo* data.	Clinical study data or case reports if available; *in vivo* animal data; *in vitro* data if no clinical or *in vivo* data available	Non-clinical and clinical data in the latter half of the phase I study or in the first half of the phase II study.

Table A.34: Key differences in the procedures for orphan designation in the EU, US and Japan

Items	EU	US	Japan
Application to	Committee for Orphan Medicinal Products (COMP).	Office of Orphan Products Development (OOPD).	Ministry of Health, Labour and Welfare (MHLW)
Timetable	Timetable for submission and assessment published by the Agency.	Any time; no defined timetable;	Any time; no defined timetable;
Key aspects of the application	Prevalence; Medical need; Medical plausibility.	Prevalence. Scientific rationale.	Prevalence; Medical need; Possibility of development.
Sponsor established in territory	Proof of establishment in EU.	Not required.	Not required.
Translations	Translations of product name and proposed orphan indication into all official languages of the EU plus Icelandic and Norwegian.	Not required.	Application in Japanese.

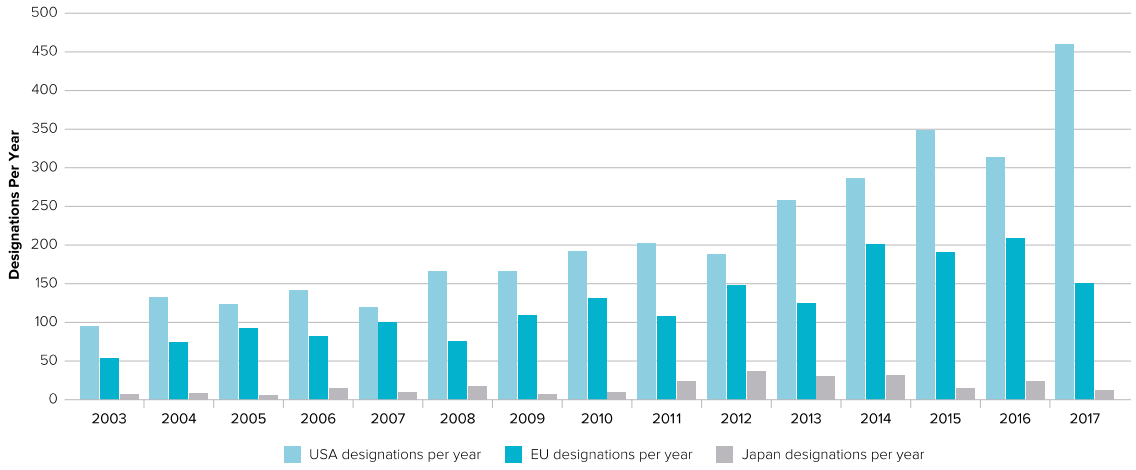
In the US, a medicinal product is eligible for orphan designation when it is intended to treat a disease that affects less than 200 000 persons (which is equivalent to 6 in 10,000) in the US or affects more than 200 000 persons and for which there is no reasonable expectation that the cost of developing and making a medicinal product for such disease or condition will be recovered from sales.[26] In addition, in the US an orphan designation may be given to an orphan subset of a non-rare disease condition where the characteristics of the medicinal product limit its use in a particular subgroup.[27]

[26] Orphan Drugs Act of 1983. Public law 97/414, 97th Congress, Jan 4, 1983.
[27] O'Connor DJ; Expert Opinion on Orphan Drugs (2013), 1(4):255-259.

Table A.35: Comparison of incentives offered by the EU, US and Japanese regulatory frameworks to support OMP development

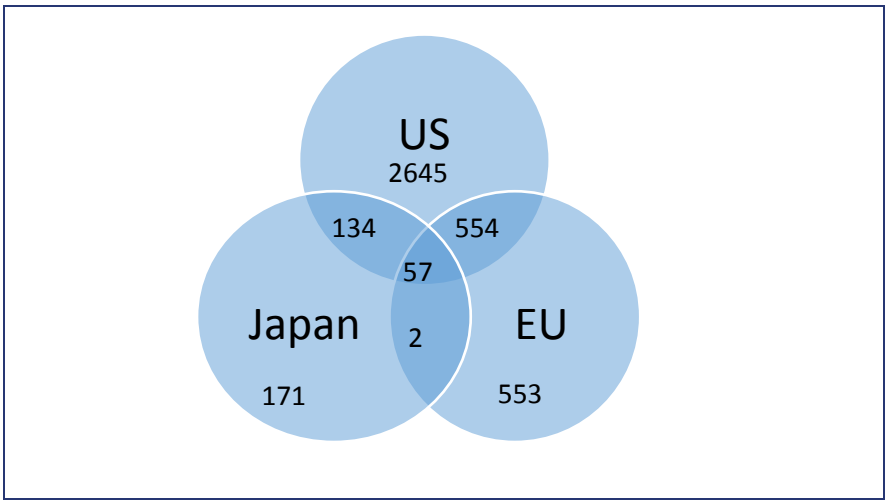
	EU	USA	Japan	Australia
Year of introduction	2000	1983	1985	1997
Financial incentives	Fee reductions / waivers	Tax credits, fee waivers	Subsidies for research, fee waivers, tax credits and reductions	Fee waivers
Market exclusivity	10 (+2) years	7 years	10 years	No
Scientific advice (protocol assistance)	Yes (free)	Yes (free)	Yes (reduced fees)	Yes
Aid for research	EC Framework Programmes	FDA Orphan Products Grant Program; NIH grants	Grants programmes	No
Regulatory tools to accelerate approval	Priority medicines (PRIME); centralised procedure; conditional approval; approval under exceptional circumstances; accelerated assessment	Fast-track approval; Breakthrough designation; Accelerated approval pathway; Priority review designation	Priority review; Fast-track approval	Possibility to rapid review

Figure A.36: US, EU & Japan Orphan Designations per Year (2003-2017)



Source: EvaluatePharma 2018.

Figure A.37: Common orphan designations in the US, EU and Japan (n=4116)



Modified from Murakami M and Narukawa M, Drug Discovery Today, (2016), 21(4):544-549