Knowledge Base Summary

Availability and accessibility of Orphan Medical Products (OMPs) and medical devices

Introduction to the Topic – the Policy context

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000) was adopted in December 1999 and came into force in the European Union in 2000, addressing the need to offer incentives for the development and marketing of medicines for rare conditions. The Regulation stipulated the definition for a rare disease in the European Union: for a medicinal product to be designated an *orphan* medicinal product, it must be intended for the treatment, prevention or diagnosis of a condition with a prevalence in the EU of no more than 5 in 10,000

This Regulation was followed by several further Regulations relevant the development and marketing of Orphan Medicinal Products (OMPs), including the following: Regulation (EC) No 847/2000 (established the implementation rules and provided definitions required for applications under Regulation 141/2000); Regulation (EC) No 726/2004 (provided the legal framework for the centralised authorisation and supervision of medicines and thus established the EMA); and **Regulation (EC) No 1901/2006** (concerning medicinal products for paediatric use, allowed OMPs to extend their exclusivity period to twelve years).

It has long been recognised, however, that the approval of an OMP does not automatically equal access for patients. Many policies and resources have a bearing on Health Technology Assessment and the availability of OMPs in national/regional health systems. Recent policies illustrate a growing shift towards pan-European collaboration here, for instance through the 2018 **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU** (see below)

Thinking specifically about *rare disease* policies, the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** includes several 'chapters' on this topic:

5.3. Access to Orphan Drugs (the bold emphasis is not present in the original)

"There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. ***The way forward is to increase collaboration at the European level for the scientific assessment of the (added) therapeutic value of Orphan Medicinal Products.*** *The Commission will set up a working party to exchange knowledge between Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines. These collaborations could lead to* ***non-binding common clinical added value assessment reports with***

improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities*. Furthermore, the involvement of the EMEA and existing international Health Technology Assessment networks as the Health Technology Assessment International (HTAi), the European Network for Health Technology Assessment (EUnetHTA) or the Medicines Evaluation Committee (MEDEV) should be considered."*

5.6. Incentives for Orphan Drug development

"Pharmaceutical companies invest heavily over a long period of time to discover, develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. ***Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State awareness with these products should be encouraged*** *in accordance with Article 9 of Regulation (EC) No 141/2000."*

(Specific chapters relating to **Compassionate Use programmes** and **Medical Devices** are included below). This theme of cooperation is also visible in the following year's **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02.** The preface emphasises *"It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the common instruments foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008 […]This could be also the case for the assessment reports on the therapeutic added value of orphan medicinal products, which could contribute to accelerating the price negotiation at national level, thereby reducing delays for access to orphan drugs for rare diseases patients."*

Further into the Recommendation, Member States (MS) are explicitly asked (in Section V: *GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL*) to
"Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: […]
(e) the sharing Member States' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge and expertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients."

EUCERD Recommendations on the CAVOMP Information Flow

With several policies therefore promoting greater cooperation between EU level authorities and MS to improve access to OMPs, in 2012 the European Union Committee of Experts on Rare Diseases (EUCERD) adopted a set of Recommendations addressed to the European Commission and Member States on ***Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow.***

The document highlights ways to facilitate scientific information exchange on OMPs, in order to support MS in making informed decisions as to the **scientific assessment of the clinical effectiveness** of an OMP. It encourages the creation of an 'Information Flow' between individual MS and between MS and the EU bodies, which would bridge knowledge gaps, especially those existing at the time of marketing authorisation. This information flow was designed to fit in to existing regulatory, clinical, Health Technology Assessment (HTA), pricing and reimbursement processes, while avoiding additional burdens. The CAVOMP information flow recommended by the EUCERD includes four time points:

- Timepoint 1: Early dialogue
- Timepoint 2: Compilation Report and evidence definition / Evidence Generation Plan (EGP)
- Timepoint 3: Follow-up of the EGP
- Timepoint 4: Assessment of relative effectiveness

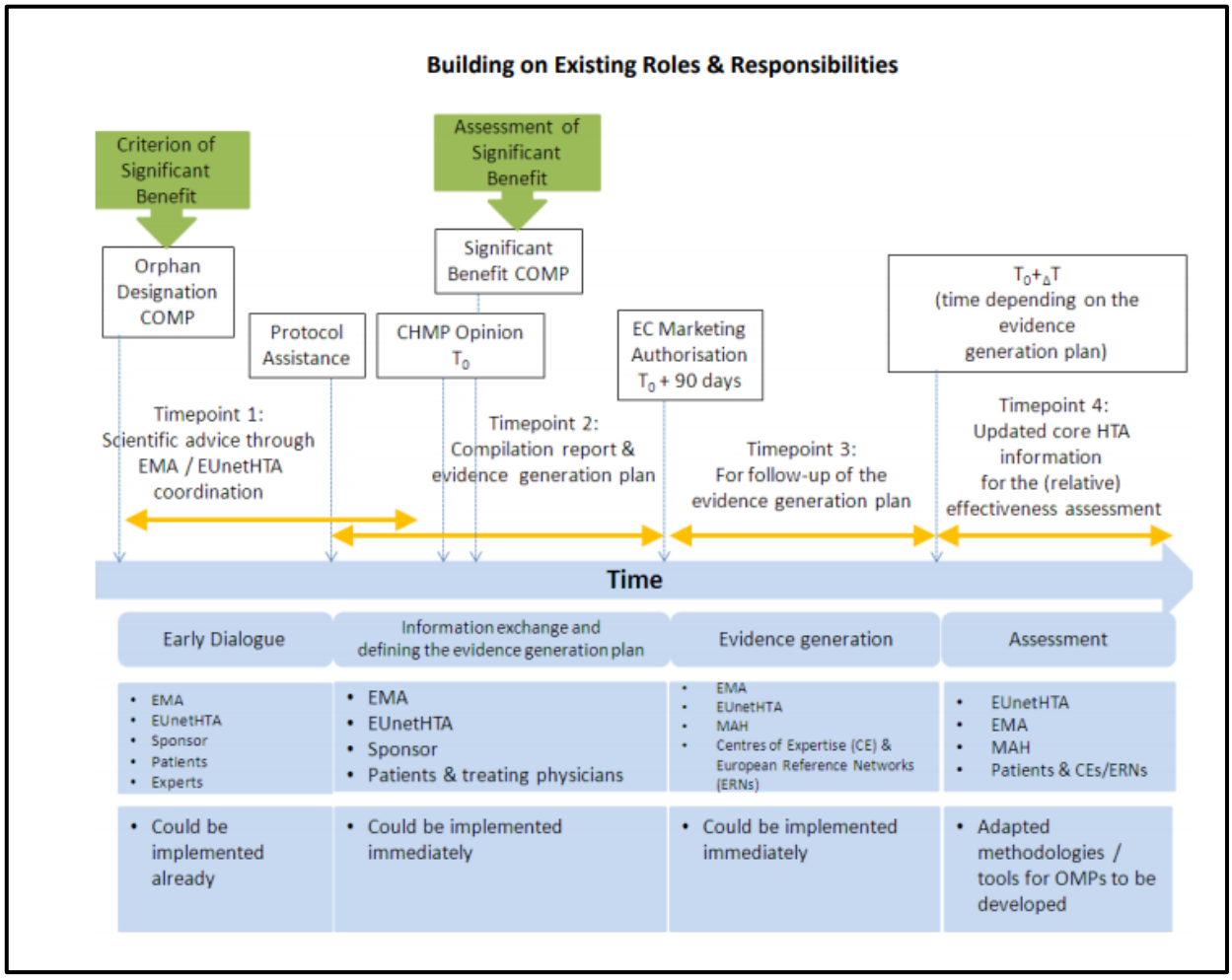


Image take from the EUCERD Recommendations on the CAVOMP-IF

Guiding Questions for Panel of Experts Discussion – to support the identification of trends and drivers of change

1. **How can we stimulate greater development and access to medical devices for people with rare diseases?**

2. **Is the current legislation affecting OMP access fit for purpose? Where could improvements be made?**

3. **What practical actions (at national and European level) would increase the accessibility and availability of OMPs?**

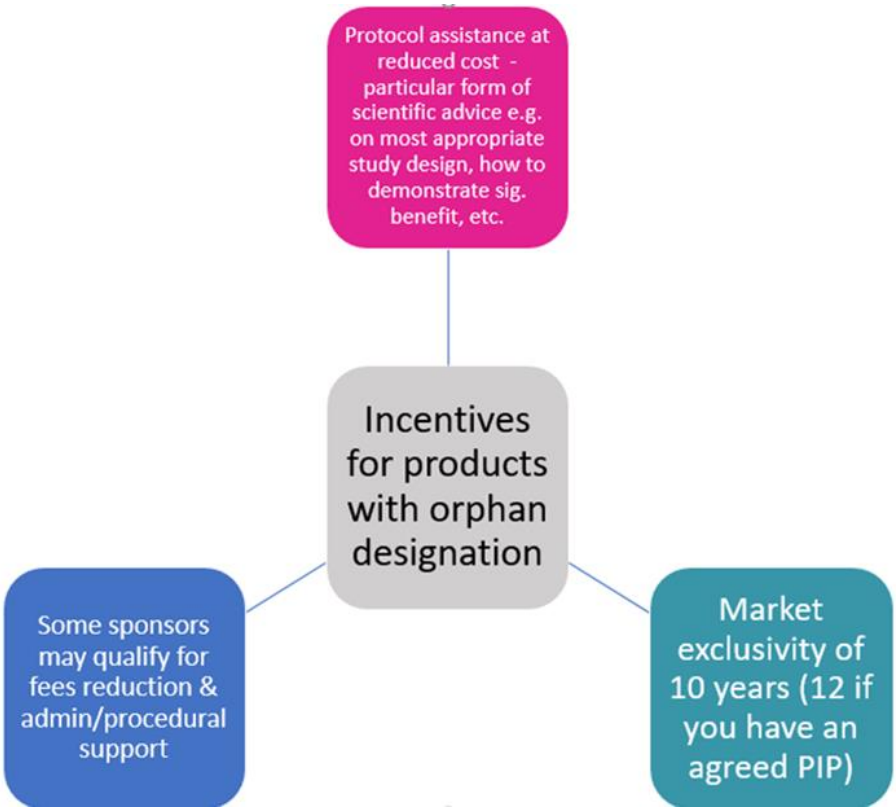
The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000) addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides incentives for products receiving an orphan designation. The process by which a medicinal product enters the market as an orphan medicinal product (OMP) involves several stages:

- A sponsor submits an application to the European Medicines Agency (EMA), seeking orphan designation for their medicinal product
- The application is evaluated by the Committee for Orphan Medicinal Products (COMP) at the EMA (the COMP was established in 2000 via Regulation (EC) 141/2000. The COMP provides an Opinion on the application, which could be positive or negative: this Opinion is then conveyed to the European Commission
- The European Commission decides whether or not to bestow Orphan Designation

There are specific criteria which a medicinal product needs to fulfil, in order to qualify for this orphan designation:

- ✓ it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- ✓ the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- ✓ no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Once ***orphan designation*** has been granted, the product attracts a range of incentives. For example:



Once a sponsor is ready to submit an application for **marketing authorisation** (MA), they are able to use a centralised procedure. The MA application itself will be assessed by the Committee for Medicinal Products for Human Use (CHMP), which will issue an opinion and convey this to the European Commission.

A set of FAQs has been issued by the EMA on the subject of orphan medicinal products and rare diseases:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/02/WC500244578.pdf

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Status Quo of OMP Designations and Authorisations in Europe

- ✓ **As of May 2019, there are currently 1643 products with active orphan designation in the EU (i.e. not withdrawn or expired)**
- ✓ **Between 2000-2018, 2121 orphan designations had been issued by the European Commission**
- ✓ **167 orphan medicinal products have received marketing authorisation**

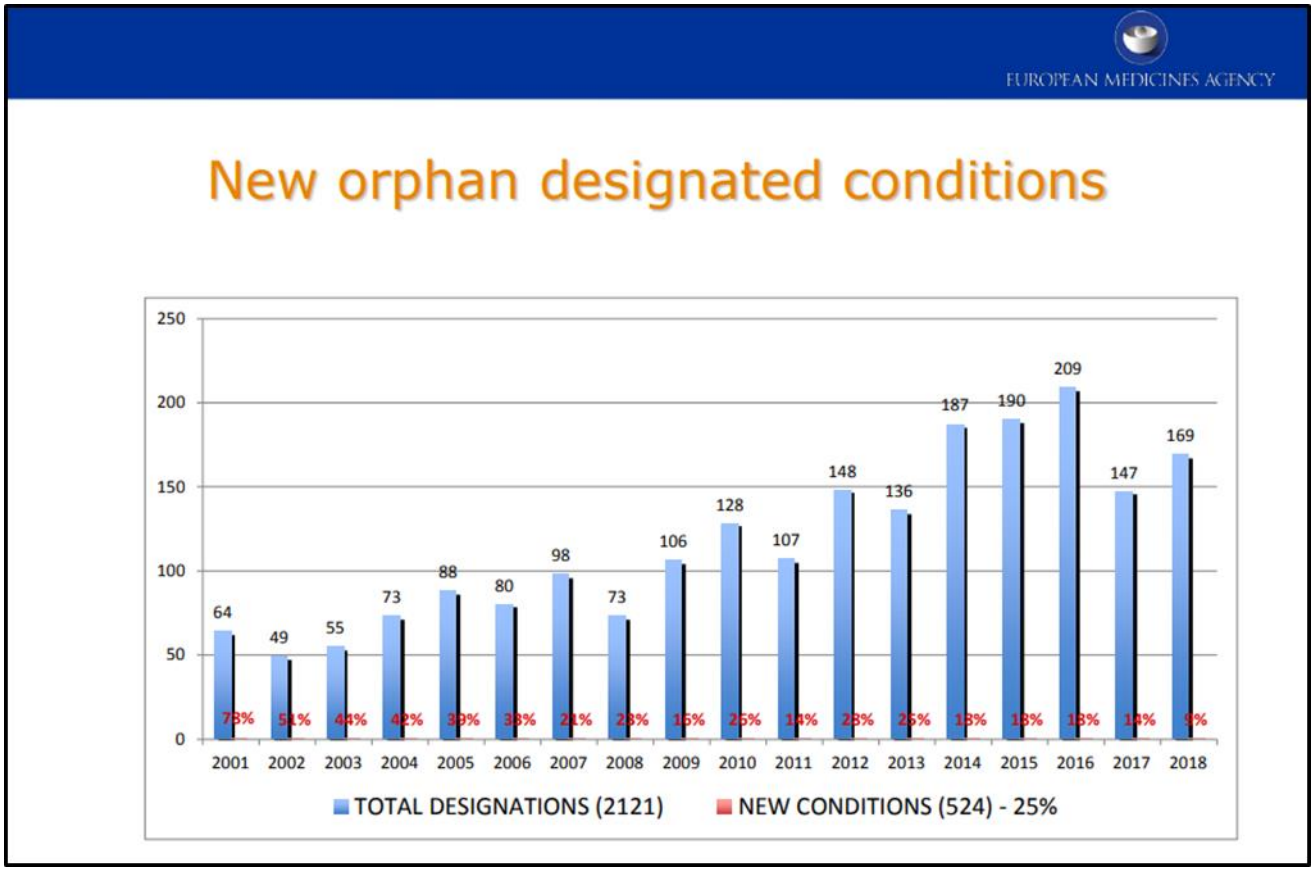
The following table from the EMA (COMP) annual report on OMPs shows the trajectory of orphan designations since 2000:

Applications for orphan medicinal product designation

	2000 2005	2006 2010	2011 2015	2016	2017	2018	**Total**
Applications submitted	548	686	1151	329	260	236	3210
Positive COMP Opinions	348	500	759	220	144	163	2134
Negative COMP Opinions	8	6	7	2	2	3	28
EC Designations	343	485	768	209	147	169	2121
Withdrawals after submission	150	144	313	77	100	92	876

EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The vast majority of new orphan designations, since 2003, have been for conditions which already have an indication. This table from the EMA (COMP) annual report illustrates the percentages of orphan designations each year awarded to new conditions

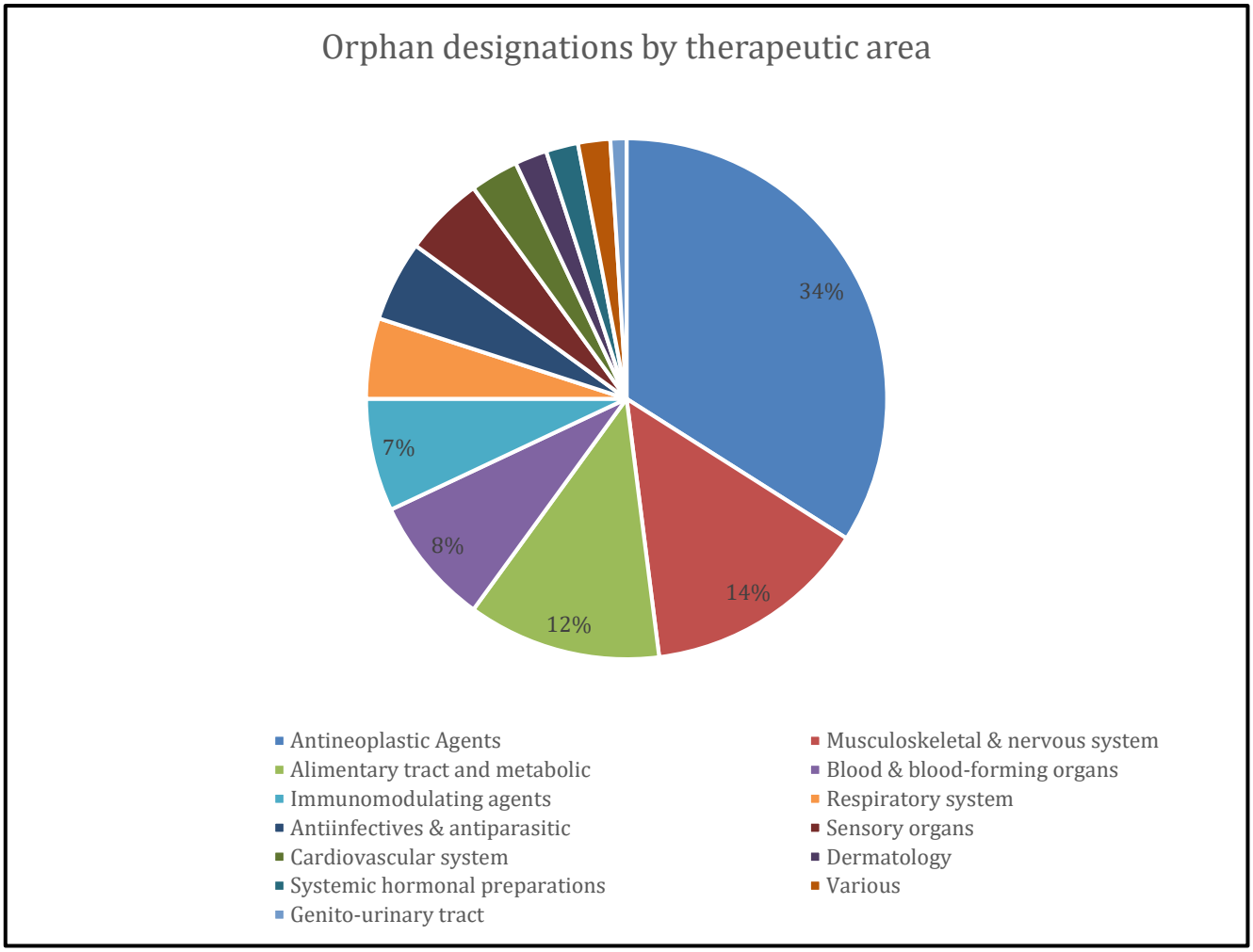


EMA image: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf

The majority of the 2121 orphan designations awarded by the end of 2018 tend to be for both **adult** and **paediatric** use (57 % according to EMA figures for 2018), with 31% for adults only and 12% for paediatrics only.

EMA statistics also illustrate that 44% of all Marketing Authorisations granted during the period 2000-2018 were for conditions with a **prevalence** of less than 1 per 10,000, meaning 56% are for those with a prevalence between 1 and 5 per 10,000. (source is https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf)

Orphan designations tend to be clustered around particular therapeutic areas, most prominently in the categories of oncology, musculoskeletal & nervous system, and alimentary tract & metabolic: the data in the pie chart below comes from the annual EMA (COMP) report on OMPs: https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2018_en.pdf



Does Marketing Authorisation equal Availability everywhere in Europe?

A major issue in the European rare disease field is that OMPs and innovative therapies which receive a central European Marketing Authorization are often *not* in fact available in all EU countries: each country determines for itself whether to make an authorised product available within the national territory, and whether to reimburse patients for using it.

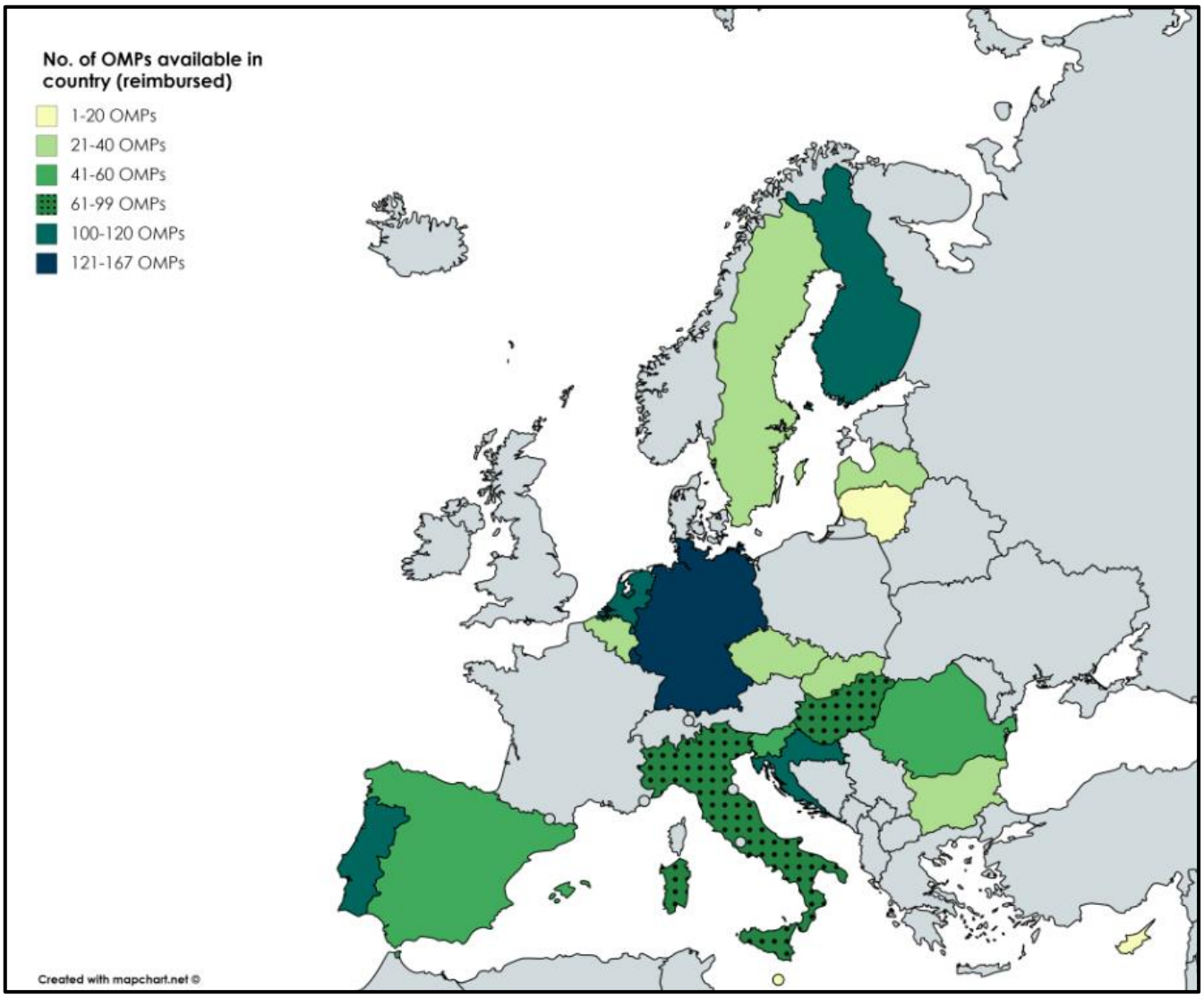
At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. This map shows the status quo as of May 2019.

The data in the map comes from the *Resource on the State of the Art of Rare Disease Activities in Europe*. Countries are asked to provide information on their national activities pertaining to rare diseases by responding to a structured survey. The questions in this survey are designed to enable countries to provide the data they pledged to submit when adopting the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans and Strategies* in 2013.

Countries were asked *"How many OMPs with a European Union marketing authorisation are available in your country (i.e. are priced and reimbursed or directly provided by your country's health system)?"*

NB:

- Please note that data for a number of countries is still awaiting update; **therefore, these figures may change slightly in the coming months** (it is acknowledged that providing this information can be challenging).
- Clarifications will be sought from some MS.
- At present, **the MS depicted in grey** have not yet provided a response to this question.



'Alternative' routes to access OMPs and innovative therapies

It is sometimes possible for patients to access OMPs which have not yet received a marketing authorisation or which are not yet reimbursed in countries – an example is **'compassionate-use'**, sometimes called 'expanded access'. For instance, if a medicine is still working its way through the research and development stage, it may be accessible via this sort of programme for a patient (or group of patients) not eligible for/not included in the clinical trial.

- ✓ Compassionate use programmes are intended for cases when the medicine is expected to help patients with life-threatening, long-lasting or seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorised medicine.
- ✓ They can be intended for cohorts, or for individuals on a named-patient basis
- ✓ **Regulation (EC) No 726/2004** outlined the concept of Compassionate Use Programmes, emphasising that the product concerned must be working toward a Marketing Authorisation or else must be undergoing clinical trials. Member States are supposed to notify the EMA of Compassionate Use Programmes they employ.

The concept of compassionate use appeared in the 2008 Commission Communications on rare Diseases: Europe's Challenges (section 5.4) as follows: *"A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs is needed. Under the existing pharmaceutical legislation, the EMEA may issue opinions on the use of the product under compassionate use to ensure a common approach across the Community. The Commission will invite the EMEA to revise their existing guideline with a view to providing patient access to treatment."*

It is important to note that, although the EMA provides recommendations, countries make their own decisions on when to permit compassionate use. The efficiency of different national systems for Compassionate Use is variable. EURORDIS published a Position Paper on Compassionate Use in 2017, designed to raise awareness of this variation and to improve the status quo

Countries can also provide off-label access to medicines, for rare diseases and otherwise. (Off-label use is when a drug is used for an indication other than those specifically included in the labelling – this can be as significant as use for a different condition, or simply use at a different time of day).

Medicines Adaptive Pathways to Patients

The concept of Medicines Adaptive Pathways to Patients (MAPPs), or 'adaptive licensing' emerged from the realisation that there is a point after perhaps a decade of research and studies when a go or no-go decision is made concerning a marketing authorisation or a reimbursement. A 'No-Go' decision at this point, after years of financial, scientific, regulatory and emotional investment in a product, is regrettable for all parties. MAPPs represent a more flexible, non-traditional approach to bringing innovative drugs to market.

The key for many is 'early dialogue', to try to avoid products failing after so many years of development time, energy and cost. The essence of MAPPs is that alternative routes to availability should be permitted on the understanding that a greater collection of data will be collected in the post-marketing phase. (Usually, after marketing authorisation, there is a decline in data collection through observational studies and registries, as the number of patients taking the drug *without* surveillance increases significantly). For instance, under some adaptive licensing scenarios, an *Initial* License may be granted following clinical trials on a smaller number of patients, on the proviso that robust monitoring continues via studies and registry data collection until a point when the confidence is assured and *full* MA is awarded.

Evaluation of European regulations on medicines for rare diseases and paediatric populations

In recent years the Orphan Drug Regulation of 2000 has come under scrutiny. In 2016, **Commission notice 2016/C 424/03** facilitated the application of Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register) and 7 (Union marketing authorisation).

In 2017, a 10-year evaluation report on the EU Paediatric Regulation was published. This report concluded that the Regulation had provided positive results overall in terms of paediatric product development, but that development for rare paediatric diseases, which is in many cases equally supported through the Orphan Regulation, often failed to materialise. Following this report, the European Commission announced a joint evaluation of the Paediatric and Orphan Regulations, due to take place in 2018-2019. The purpose of the evaluation is to provide an assessment of the strengths and weaknesses of the two Regulations, separately and combined, and to give insight in how the various incentives of the Regulations have been used and what the financial consequences have been. This information will be used to consider the possible need for future changes to the Regulations. The public consultation phase of this evaluation closed in early 2019, and a targeted consultation of stakeholders took place in June 2019. **The final report is due at the end of 2019.**

Health Technology Assessment for rare diseases

National (sometimes regional) Health Technology Assessment (HTA) bodies issue recommendations on health technologies to the healthcare system of a particular Member State or region. HTA is often associated with pharmacological products; however 'health technology' is actually a very broad term and includes medical and surgical interventions, medical devices, diagnostic tests, etc. HTA can include both clinical and non-clinical assessments of added-value.

In many EU countries, the decision on what to *do* with these assessments (e.g. determining whether to make a product available for reimbursement, and if so establishing the price) is usually made by payers; in other words, HTA is rooted in research and the scientific method, as opposed to price. A major cause of heterogeneity in levels of access to medicinal products is that generally speaking, the centralised European procedure ends with the marketing authorisation, whereas assessment of therapeutic value, pricing, and reimbursement decisions are handled by MS on an individual basis. There are many consequences to this, which each affect the availability of OMPs:

- For instance, when facing potentially 28 separate negotiations, Companies may prefer to first launch products in wealthier countries, establishing a benchmark too high for lower GDP countries to reach.
- National decisions on HTA are made very differently from country to country, even for the same product. A 2016 study (Kawalec et. al) analysed such decisions for the first 93 OMPs authorised in Europe: 23 of these had not been assessed in at least one of the countries.
- There appears to be ***no clear*** correlation between the assessment of value and the accessibility of the therapy through national reimbursement channels: the aforementioned study showed that despite a positive assessment in 50% of cases, the rate of reimbursement was significantly lower. In short, not all OMPs receiving positive assessments actually end-up

on reimbursement lists, whereas some negatively assessed products *will* be marked for reimbursement.

Many stakeholders have called for greater clarity and transparency in understanding the decision-making process around HTA in different countries.

European HTA Cooperation:

For many years, there have been calls to promote collaboration between countries on certain aspects of the HTA process.

- ✓ Art.15 of the 2011 Cross-border Healthcare Directive (2011/24/EU) called upon the EU to support and facilitate cooperation between national HTA bodies.
- ✓ The Health Technology Assessment Network was established (as a voluntary network) through an Implementing Decision in 2013, aimed at increasing scientific and technical cooperation.
- ✓ This network was supported by 3 successive EUnetHTA joint actions which have worked towards the piloting of joint assessments of relative effectiveness.
- ✓ In 2018 the European Commission published a **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU**

The proposal for a new Regulation on HTA centres around common tools, methodologies and procedures across 4 areas:

1) Joint clinical assessments for innovative health technologies
2) Joint scientific consultations to enable developers to seek advice from HTA authorities
3) Horizon scanning/identification of emerging health technologies
4) Continuing voluntary cooperation in other areas.

Under the proposal, each individual country retains responsibility for the non-clinical aspects of HTA, and would continue to make all decisions pertaining to reimbursement and price. **The proposed Regulation would cover medicinal products but also certain medical devices**

The table below presents a VERY select overview of some past and ongoing initiatives, projects or resources with a particular relevance to this topic

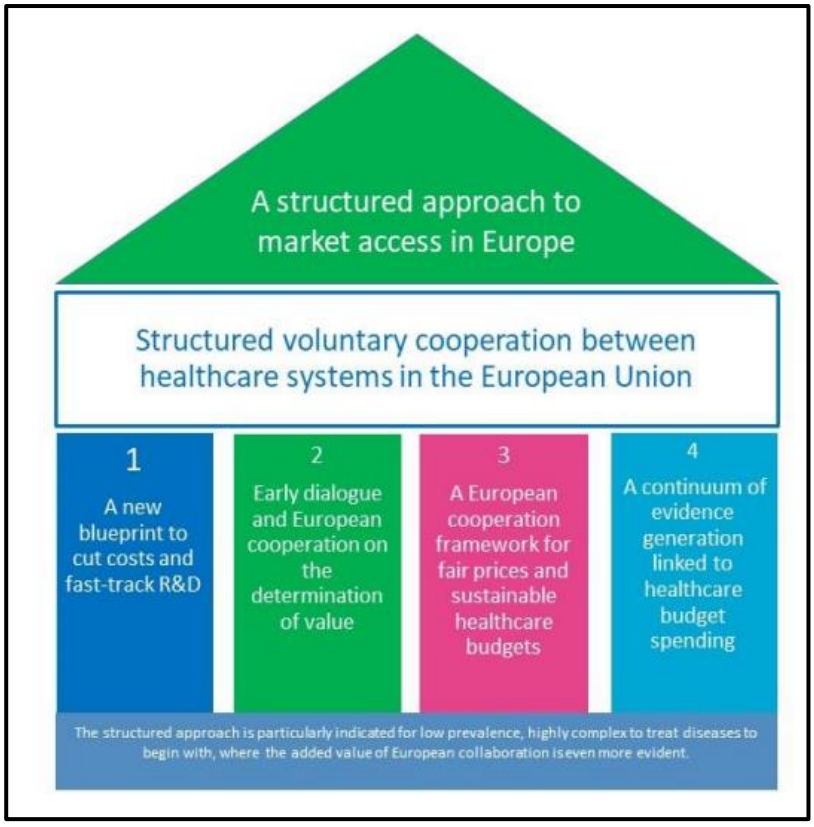
Initiative/Resource	Scope and Outputs
The Mechanism of Coordinated Access to OMPs (MoCA-OMP)	An initiative uniting patients, payers and companies. Created a tool called the 'European Transparent Value Framework', which is designed to structure discussions around the value of individual OMPs. MoCA was specifically focused on OMPs
'Breaking the Access Deadlock to Leave No One Behind'	A 2018 Position paper by EURORDIS and its members to propose possibilities for patients' full and equitable access to RD therapies in Europe. (see below)
EUCERD Recommendations on the CAVOMP-IF	As above – The Recommendations on ***Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow*** were adopted by the EUCERD in 2012.
'Early access to medicines in Europe: Compassionate use to become a reality'	A 2017 Position Paper on Compassionate Use from EURORDIS. Includes Recommendations to Industry; to national and European authorities; and to patients' organisations and healthcare authorities
European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)	ORPH-VAL was a collaboration between rare disease experts, patient representatives, academics, health technology assessment (HTA) practitioners, politicians and industry representatives. It produced Recommendations in 2017 on 4 areas: OMP decision criteria; OMP decision process; OMP sustainable funding systems; and European co-ordination
The European Network for Health Technology Assessment (EUnetHTA)	EUnetHTA as an entity was formed in 2006. Since 2010 it has been supported as three successive European Joint Actions (the 3rd will end in 2020). EUNetHTA was established to harness synergies between regulatory evaluation and HTA along the lifecycle of a medicine. Outputs include shared tools such as the HTA Core Model®, a methodological framework for production and sharing of HTA information. EUnetHTA is not specific to rare diseases.
Health Technology Assessment Network	The HTA Network was established in 2013 answer to Art. 15 of the Cross-Border Healthcare Directive (2011/24/EU). All EU countries are represented. The goal is to provide strategic and political guidance to the scientific and technical cooperation of HTA at EU level.
ADAPT-SMART	This project –funded by the Innovative Medicines Initiative, from July 2015 to April 2018- investigated MAPPs tools and methodologies, engaging in dialogue with all relevant stakeholders to prove and develop MAPP concepts. ADAPT-SMART was not specific to RD but has a clear relevance to this community. Results are available here
PRIME	PRIME is an EMA initiative to enhance support for the development of medicines that target an unmet medical need. The scheme is voluntary and centres upon early dialogue and stronger interactions with developers, through scientific advice. It seeks to improve trial design to generate better data more suited to the MA application. PRIME is not specific to OMPS but includes medicines for RD

2018 EURORDIS Position Paper

In 2018, EURORDIS and members issued a position paper 'Breaking the Access Deadlock to Leave No One Behind'. The paper is designed to address the issues around availability and accessibility to OMPs, as part of EURORDIS' ambition to have 3 to 5 times more new rare disease therapies approved per year, 3-5 times cheaper, by 2025.

The position paper outlines a framework composed of 4 pillars.

It concludes with a number of key recommendations to 'break the deadlock':



(Image from the 2018 EURORDIS position paper)

- All EU Member States already engaged in multi-country cooperation platforms should accept to join voluntarily to establish the "European Table of Negotiation". If not all EU27, a significant number will create a population critical mass enabling to address the challenge of rarity, hence immediately becoming the pivotal partner for negotiations and launching a dynamic.
- All EU Member States on board the "European Table of Negotiation" should commit to examining, in an open multi-stakeholder format, the innovative approach to lay out a more transparent pathway to the construction of prices (based on costs, compounded by a determination of the value of the product, and adjusted by premiums and discounts as relevant).
- All EU Member States on board the "European Table of Negotiation" should commit to entering into Joint Price Negotiations or Joint Purchasing as the next step – if only for orphan medicines at the beginning – and to formalising the outcomes of these negotiations into Managed Entry Agreements with manufacturers.
- All EU Member States on board the "European Table of Negotiation" should commit to exploring much further the feasibility of applying differential pricing mechanisms to the agreed "European Transactional Price", as a means to tailor the said price to their respective levels of purchasing power and domestic wealth.
- All EU Member States on board the "European Table of Negotiation" should commit to considering discounts for uncertainties, payments based on outcomes, formative HTA assessments and all other appropriate modalities or techniques so as to provide early patient access to medicines approved under exceptional circumstances, under conditional approval, at the end of stage 2, or in any other situation when uncertainties are high or significant

Global legislation around OMPs

In the US, the Orphan Drug Act has been in place since 1983. It provides orphan drug designation for medicines, biologics, or medical foods intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders which affect fewer than 200,000 people in the US, or which affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. There are currently more than 3500 products with active orphan designation in the US (i.e. not withdrawn). As of the end of 2018, over 600 orphan drugs had been approved. A search of the FDA site shows over 800 instances authorisations (including some instances of the same product authorised for new indications) (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

Following the success of the US Orphan Drug Act, a number of other countries (outside of Europe) have also implemented orphan drug policies, including Singapore (1991), Japan (1993, update of earlier RD legislation), Australia (1997), and Taiwan (2000) (for further details see the 2018 Overview Report from the Resource on the State of the Art of Rare Disease Activities in Europe, p23 onwards)

Medical Devices for Rare Diseases

'Medical Devices' as a term, is incredibly broad. Over 500,000 devices are on the market in Europe, including medical software. The first legislation in Europe for Medical Devices emerged only in the 1990s, and began operating via the existing system of 'notified' bodies ('Notified' bodies are national bodies recognised and authorised to perform assessments of products – countries 'notify' the EC 'of these bodies, which are then added to the NANDO database (which contains hundreds of such bodies).

Medical Devices are very important for people with rare diseases, an importance which is arguably *heightened* by the absence of a dedicated medicinal treatment for 95% of the conditions classed as rare. Specialised devices can make a huge difference to the diagnosis, treatment, care and quality of life of this population; however, the cost of (particularly customised) devices can be prohibitive and, as is the case for OMPs, they may not be included in an appropriate reimbursement system.

The topic was incorporated to the **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** as follows:

5.5 Medical devices: *"The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Devices Directives."*

In April 2017, two new regulations for Devices were adopted:

- Regulation (EU) 2017/745 on medical devices;
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices

Entering into force in May 2017, these Regulations replace the previous Directive (Directive 93/42/EEC concerning medical devices) meaning their contents are directly applicable at national level without requiring transposition through specific national legislation. One of the main strengths of the new

legislation is **greater emphasis on greater clinical evidence**, as opposed to only safety and risk/benefit ratio. There is also stronger emphasis on post-marketing surveillance for devices. However, issues remain; for instance, notified bodies do not need to publish their clinical evaluation assessments, meaning there is a lack of transparency. Most European countries treat pharmaceuticals and devices desperately, through entirely different agencies and units, in fact.

Despite the improvements offered by Regulation (EU) 2017/745, there is no European agency for medical devices – i.e. no equivalent of the EMA – to perform centralised reviews and authorisations. The EU is supposed to support the process; however, the main activity here will likely be the launch of the second generation of the EUDAMED (European database on medical devices) database, expected in 2020. There is also no European process for the conditional approval of devices: notified bodies are able to grant this, but supposedly only upon assurance of a robust data-collection strategy and data submission after 12 months, which may not in fact materialise.

Unlike in the case of OMPs, there are no incentives in the existing European legislation for the development of medical devices intended specifically for rare diseases. The United States, by comparison, has a 'Humanitarian Use Device' exemption for devices intended for conditions affecting/manifesting in no more than 4000 people in the US each year.

The 2018 **Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU** which aims at supporting a European approach to HTA clinical assessments includes a selection of Class II, IIIb, and In-vitro diagnostics Devices.

Repurposing of Medicines

Drug repurposing is a good example of innovation in research and care – it centres upon the use of a rigorous scientific process to find new ways to make use of existing medicinal products. Greater understanding of the underlying causes and biochemical pathways responsible for rare diseases opens up opportunities to use existing medicines to address impairments and errors. Drug screening and data mining approaches can identify promising candidates. Repurposed medicines carry the advantage of a strong safety profile, and although preclinical and clinical studies may still need to be performed in the newly-intended community, the extent and therefore the costs of such activities are often lower than developing a brand new medicine from scratch (there will usually be robust data on the pharmacokinetic performance, for instance).

Groups such as Findacure are raising awareness of repurposing opportunities in the rare disease community (and indeed are accelerating these). At European Level, the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) is currently focusing on the potential of repurposing

Results of the Rare2030 literature review

As a consequence of the commercial unattractiveness of orphan medicinal products, one can observe a diversity **of incentive policies**, most notably in Europe or the United States, in order to guarantee the availability of orphan medicinal products (Annemans et al. 2017; Gong and Jin 2012). Indeed, the nature of rare diseases, affecting few and scattered patients, induces high costs for orphan medicinal products and is often viewed as a serious burden for healthcare systems. In addition, the current economic crisis and tendency to reduce public spending strengthen the hurdles for their development. The small population concerned as well as the substantial research costs associated with orphan medicinal products are also great impediments to research in the field of rare diseases (Gammie et al. 2015).

Two types of incentives can be distinguished: push and pull incentives. Push factors comprise various mechanisms such as the allocation of subsidies for research, tax credits, intellectual property rights, patent buyouts, public innovation funding and grants and fast-track procedures. Pull incentives include mainly long market exclusivity and authorisation criteria. Most of these are present in Europe and the United States and some are also applied in China, demonstrating the global characteristic of this trend (Gong and Jin 2012; Patel and Miller Needleman 2019).

Moreover, as a means to regulate the availability of orphan drugs and the orphan drug market, countries tend to establish regulatory agencies such as the Committee for Orphan Medicinal Products or the US Food and Drug Administration, which offer a framework for and facilitate research on treatments for rare disease (Gammie et al. 2015). Pieces of legislation are gradually drafted and implemented - cf. Regulation (CE) N°141/2000 for the European Union and the 1983 Orphan Drug Act for the United States - to enhance orphan drug research, development and marketing (Gammie et al. 2015; Wellman-Labadie and Zhou 2010) .

Besides the public efforts to incentivise the production of new orphan drugs, the **state of the market and the technological advances** can also act as drivers attracting certain pharmaceutical companies towards rare diseases (Mingorance 2018). In fact, the unfavorable and competitive market conditions, specificities of rare diseases combining the absence of drugs and high clinical unmet needs, and technological innovations in genomics, push small, technology-focused companies to invest in orphan drug development, pushing them away from the canonical “blockbusters” research programmes (Attwood et al. 2018; Mingorance 2018). Nonetheless, the **maturity of the drug pipeline also needs to be taken into account** when examining the attractiveness of rare diseases (Mingorance 2018).

As a whole, the more general trend which emerges out of the association of all these phenomena is a **reasonable availability rate of orphan drugs, at least in Western and economically influential regions of the world, but at a very high price** (Hughes-Wilson et al. 2012).

This creates an issue in terms of **real accessibility of such treatments which is utterly different from their availability** (Blankart et al. 2013) **and is particularly heterogeneous**. Indeed, reimbursement policies vary across Europe regarding the share of reimbursed orphan drugs and the possibility of direct provision by healthcare systems. A schism exists between countries of Western and Eastern Europe but also among European countries and within the same country (Bourdoncle et al. 2019;

Deticek et al. 2018; Korchagina et al. 2017; Pejcic et al. 2018; Szegedi et al. 2018). As a result, a trend pushing for **harmonisation of orphan drug reimbursement and prices in Europe** can be observed. As a matter of fact, market exclusivity is an effective measure to foster drug availability but can be detrimental to patient access when pharmaceutical companies benefit from this exclusivity to maintain a high price when the costs of development have already been compensated (Blankart et al. 2013; Waxman et al. 2019). Indeed, as the spending on orphan medicinal products as a proportion of GDP and healthcare expenditure is similar between lower and higher income countries, those with fewer resources cannot guarantee the same level of accessibility to these products (Szegedi et al. 2018). As such, one can distinguish a trend challenging the efficacy of legislation around orphan medicinal products as some practices of companies are seen as abuses of dominant position and generate inequity in patient access (Blankart et al. 2013; Waxman et al. 2019; Wellman-Labadie and Zhou 2010).

The variation in reimbursement rates and policies therefore suggests the need and prompts a call for **new assessment methods** and a different prioritisation of criteria for reimbursement. Our literature review showed a trend towards a re-evaluation of the standards in place **challenging the most common cost-effectiveness threshold test**, a gradual **incorporation of social preferences**, an **acknowledgement of the importance of disease and socio-economic burden for decision-making** as well as a desire to **tailor health technology assessments to the specificities of orphan drugs** (Annemans et al. 2017; Hughes-Wilson et al. 2018; Iskrov et al. 2016; Nicod et al. 2017; Rizzardo et al. 2019). Others also describe the l**ack of mutual understanding between payers and manufacturers** and **lack of transparency for orphan drug prices** (Annemans et al. 2017; Waxman et al. 2019).

Furthermore, the high cost of orphan drugs and their impact on the public budget creates a problem of potential shortages of orphan drugs and a serious challenge to patient care (Jaroslawski et al. 2016). Our horizon scanning regarding this issue indicates that some alternatives are being explored to limit the risks of shortages and increase the number of treatments and therapies. For instance, some researchers study the possibility of **drug repurposing, generic substitution, off-label use and early-access and advanced therapy medicinal products are being incentivised by a specific regulation implemented by the Committee for Orphan Medicinal Products** (Balasubramanian et al. 2016; Di Paolo and Arrigoni 2018; Dooms 2016).

Finally, the last trend detected concerns the **involvement of patients for drug development.** Studies show that they would appreciate the **incorporation of patient experiences for coverage decision-making** and to improve care and raise awareness of rare diseases, which is currently used as a means to reduce uncertainties in clinical benefit (Menon et al. 2015; Young et al. 2018).

***Possible* trends emerging from the Literature Review:**

- public incentives
- establishment of regulatory bodies and legislation
- market changes and technological innovations
- inequity and heterogeneity of patient access
- questioning of the efficacy of OMP legislation - commercial abuses
- call for new assessment methods and prioritisation for reimbursement decision-making

- involvement of patients in drug development processes

Possible **drivers of change emerging from the Literature Review:**

- market/economic conditions
- technological innovation

References from the rare disease literature review

Full list of articles/publications found in the literature review:
https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjIhGphULI/edit#gid=364400914

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