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Driving Access to Rare Disease Treatments in Europe

By Pascaline Faivre

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Gaining market access to rare disease treatments in the European Union (EU) has been challenging for pharmaceutical companies. This white paper will share some potential solutions for engaging with payers and regulators earlier and entering partnerships to accelerate patients' access to innovative drugs.

Introduction

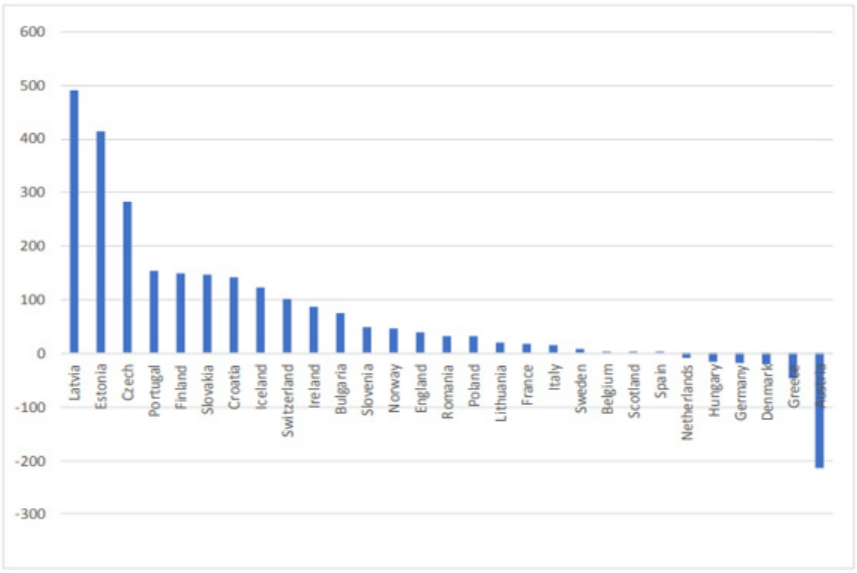
Worldwide, the orphan drug market is expected to grow at a double-digit rate of 12.3% from 2019-2024, which is double the rate of non-orphan drugs. This quick growth will inevitably pose challenges to payers who will have to absorb the budget impact of these often very expensive treatments. In Europe, market access for rare disease treatments remains a challenge for pharmaceutical companies facing difficult pricing negotiations with payers. For example, in August 2021, bluebird bio exited the European market as they were unable to reach consensus with health authorities on pricing for their gene therapy, Zynteglo.

Challenges

Time to market access in Europe is a challenge for orphan drugs as well as non-orphan drugs. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has published reports on this topic over the past few years, and their analysis shows that time to access for orphan drugs is shorter than non-orphan drugs in only six European countries (Netherlands, Hungary, Germany, Denmark, Greece, and Austria). (Figure 1) In addition, there is a trend showing longer time to access in Eastern Europe versus Western Europe. There are several root causes for this longer time to access: late initiation of the market access submission, data requirements, regional processes in addition to national, pricing negotiations dragging out for long time, etc.

Figure 1.

Difference in the median time to availability for all medicines vs orphan medicines (2015 – 2018) Positive means market access for orphan drug is slower than all medicines by a certain number of days.



Source: EFPIA report https://www.efpia.eu/media/554527/root-causes-unavailability-delay-cra-final-300620.pdf

Beyond time to access, pharmaceutical industries face several challenges when launching a rare disease treatment in Europe: lack of value recognition, lack of flexibility from Health Technology Assessment (HTA) bodies on trial design and outcomes, and barriers to early access schemes and innovative agreements.

Value recognition is a challenge for rare disease treatments as their cost is perceived as high by health authorities and poses an immediate budget impact. The uncertainty around the long-term appreciation of benefits weighs in the pricing decision.

Officially HTA bodies are more inclined to be flexible on clinical trial designs for orphan drugs. For example, they are more likely to accept a less robust design than for non-orphan drugs due to the limitations of population size, difficultly in collecting endpoints, etc. However, recent HTA evaluations of gene therapies in Europe show consistent pushback on the lack of direct and indirect comparison, short follow up, or immature overall improvements in survival (Figure 2). This implies that payers are uncertain about the long-term benefits of the treatment relative to price.

Figure 2.

HTA assessments of gene therapies in EU

HTA feedback on gene therapies - lack of flexibility

	Zolgensma (Onasemnogene abeparvovec) Novartis	Zynteglo (Betibeglogene autotemcel) Bluebird Bio	Kymriah (Tisagenlecleucel) Novartis	Yescarta (Axicabtagene ciloleucel) Gilead	Orkambi (Lumacaftor-ivacaftor) Vertex Pharmaceuticals
Date of MA (EMA)	18/05/2020	29/05/2019	22/08/2018	23/08/2018	19/11/2015
Indication	Spinal muscle atrophy (SMA)	Beta thalassemia (pediatrics and adults)	• Relapsed or refractory B-Cell acute lymphoblastic leukemia (r/r ALL) • Diffuse large B-Cell Lymphoma (DLBCL)	• Primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy • Diffuse large B-Cell Lymphoma (DLBCL)	Cystic fibrosis in patients (≥ 6 years) who are homozygous for the *F580del* mutation in the cystic fibrosis transmembrane conductance (CFTR) gene
HTA Assessments					
G-BA	After exceeding the €50 million sales threshold for orphan drugs the benefit assessment for Zolgensma followed a regular benefit assessment (without regarding orphan status) and resulted in 'no additional benefit' for all patient groups.	Not quantifiable additional benefit, due to insufficient clinical data (Reassessment requested May, 2025) Withdrawn from Market April 2021 due to price set by arbitration board.	Not quantifiable additional benefit, due to insufficient clinical data, for both indications r/r ALL and DLBCL (1st HTA assessment: 17.09.2020; reassessment on Sept 1, 2023).	Not quantifiable additional benefit, due to lack of clinical data, for both indications DLBCL and PMBCL (1st HTA assessment: 02.05.2019 (Reassessment on May 15, 2022).	For patients ≥ 6 years • Not quantifiable benefit due to uncertainty in the outcome of one endpoint • (HTA Assessment: 02.08.2018) For patients ≥ 2-5 years • Not quantifiable additional benefit due to lack of clinical data (extrapolated evidence was submitted) • (1st HTA Assessment: 15.08.2019; Reassessment: March 18, 2022)
NICE	Recommended in the context of national commissioning by NHS England (final NICE recommendation on June 4, 2021).	Not recommended in the context of national commissioning by NHS (pending final NICE recommendation)[1].	Conditional recommendation, available under Cancer Drug Fund. Immature survival data and lack of comparative data, reassessment in 2023.	Conditional recommendation, available under Cancer Drug Fund. Lack of comparative data, reassessment in February 2022.	Not recommended within its marketing authorization due to use of an acute endpoint (when longitudinal was more appropriate) and high ICER (although it was made available for use within NHS England in 2019).
HAS	SMA type I and II • ASMR İİI • SMR Important Type III SMA • ASMR V • SMR Insufficient (18.12.2020)	ASMR III SMR Important (for 12-35 years old) SMR Insufficient (for age >35 years) (18.03.2020)	ALL (22.02.2019) • ASMR III • SMR Important DLBCL (22.02.2019) • ASMR IV • SMR Important	ALL and DLBCL (22.02.2019) • ASMR III • SMR Important	For ≥ 12 years old (12.10.2016) • ASMR IV, SMR Important For 6-11 years (22.02.2019) • ASMR IV, SMR Important For ≥ 2 years old (18.09.2019) • ASMR IV, SMR Important
Key learning(s)	Lack of direct and indirect comparison	Lack of direct and indirect comparison, short FU, concerns around relevance of endpoints	Lack of direct and indirect comparison, immature OS, short FU	Lack of direct and indirect comparison, short FU	Submission of extrapolated evidence, uncertainty in endpoints used, high ICER

Potential Solutions

Despite challenges for access to rare disease treatments in Europe, solutions exist to help pharmaceutical industries and payers to collaborate early in drug development.

Early Engagement

European nations provide formal national advice to support discussions with health authorities (HA) during clinical development (Figure 3). When pharmaceutical industries submit an application, the process can take 90 to 120 days depending on the country. The objective is two-fold: gather inputs on the trial design, endpoints, modeling and put the product on the radar for the payers.

Beyond national formal advice, the EU provides joint scientific consultation for all member states. In 2021, a first call for applications was opened, and a second one is opening from June 6 to August 31, 2022. The following criteria for a drug must be met for it to receive joint scientific consultation: unmet medical needs (no treatment or only unsatisfactory treatments available), first in class, significant potential impact on patients, public health or healthcare systems, significant cross-border dimensions, and major union-wide added value or impact on clinical research priorities. The committee will select drugs based on prioritization criteria, i.e., drugs targeting a life-threatening or chronically debilitating disease and breakthrough technologies.

For drug programs in early-stage development and who meet the criteria, the EU joint scientific consultation is an opportunity to gather input on the development program. Because the UK is out of scope, seeking a parallel National Institute for Health and Care Excellence (NICE) formal early consultation is advised.

Early Access Schemes

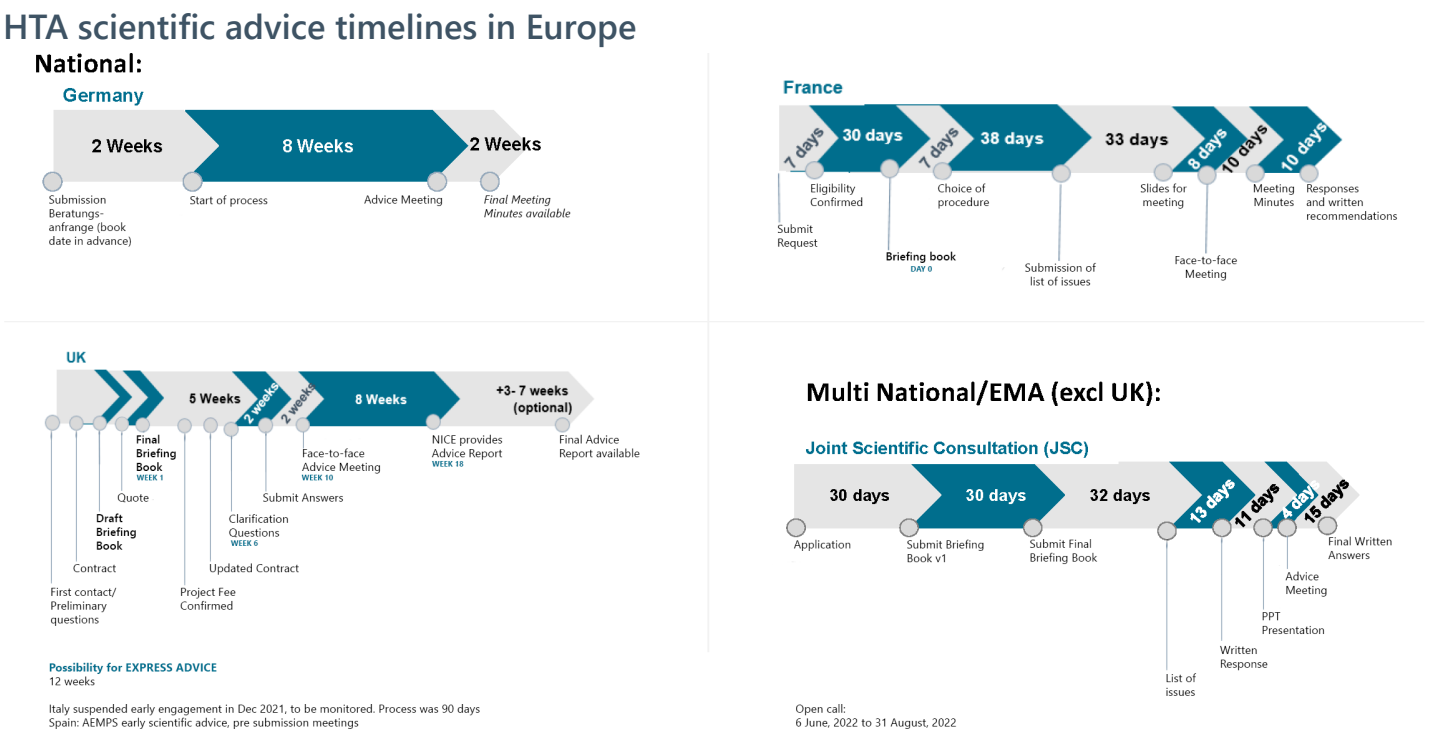
Early access schemes aim to accelerate market access while still being under European Medicines Agency (EMA) evaluation and/or HTA bodies. The schemes are country-specific. In 2016, the EMA set up PRIME (a scheme for priority medicines) to accelerate evaluations of innovative drugs. Since its establishment, 95 requests have been granted, among which 18 received EMA approval. 89% of the drugs that received EMA approval were for orphan drugs.

In Europe, the key EU countries provide early access programs.

In France, the so-called temporary authorization for use (ATU/RTU) system was replaced in 2021 to simplify and accelerate access to innovative drugs. The new system ("early access and compassionate use") is available for drugs meeting selection criteria. An application can be made before EMA approval or after EMA approval (before the Transparency committee reimbursement decision). The pharmaceutical company must apply for EMA approval within two years after early access is granted. The old and new systems will co-exist until June 2022. Currently 158 drugs are under the former ATU/RTU and new system. In France, the drug payments are funded by public funds during early access.

In the UK, early access to medicine scheme (EAMS) was implemented in 2014. The company must pay for the drug while it is being used under this program. The UK recently launched innovative licensing and access pathway (ILAP) in 2021. ILAP is a combined regulatory and access framework allowing pharmaceutical industries to access early discussions on both regulatory and market access. Since its launch, 41 of the 71 drugs that applied received the innovation designation allowing them to proceed with defining a target product profile (TPP).

Figure 3.



Innovative Contracting

Innovative contracting is a form of partnership between pharmaceutical companies and health authorities. To alleviate uncertainties on a drug's benefits, pharmaceutical companies and HA enter a financial agreement based on discounts (simple agreements) or based on clinical outcomes. A 2020 report from Alnylam summarizing findings from payer research showed that payers acknowledge barriers to setting up such agreements, namely limitations in data sharing and outcomes measurements. That said, payers expect these innovative models to become used more often as budget constraints arise and new innovative therapies emerge. A few examples of such agreements exist in Europe. Kymriah (tisgenlecleucel) was approved in 2018 for treating diffuse large B cell lymphoma. In this indication, Novartis set up agreements in France, Germany, Italy, Spain, and the UK. In Spain and Italy, a pay for performance agreement was set up based on patient response or survival. Payment was made in two or three installments if the drug showed efficacy. Kymriah is priced around 300,000 euros. In France, Germany, and the UK, coverage with evidence has been granted. Kymriah is reimbursed under the requirement that the pharma company collects more data through real world evidence (RWE) or registries. The drug will then be reassessed based on this RWE.

Real World Evidence

Real world evidence is becoming more and more important in regulatory and HTA decisions.

RWE is being used in rare and orphan drug situations in multiple ways for example:

- Registries/RWE being used for comparison purposes – in both regulatory and HTA submission/negotiation processes to demonstrate improvement in patient reported outcomes (PROs), use historical data for demonstrating clinical and economic value, and identify relevant outcomes that may be the focus of a regulatory/HTA process
- Quantifying the burden of disease
- Clinical and economic value
- Outlining diagnostic pathways, patient journeys, treatment patterns etc. as these can be varied in rare and orphan diseases and may result in delayed time to receive care, economic and clinical outcomes. This is primarily the case because of lack of treatments for these diseases. The impact of bringing a treatment on the market and improving clinical and economic outcomes is almost never quantified.
- Understanding willingness to pay or societal willingness to pay to showcase the differential in pricing offered by regular/specialized HTA frameworks and alternate valuation techniques

At the EU level, DARWIN EU project has been setup and will become operational in 2024. It aims at supplying regulatory bodies like EMA and national regulators with RWE to inform decisions. From an access perspective, NICE has recently published their new guidance for methodologies and topic selection and in it, stated "NICE will expand on and improve how it considers real world evidence."

Conclusion

Access to rare disease treatments in EU has been challenging. However, solutions exist to engage early with payers and regulators and enter partnerships to accelerate access to innovative drugs.

- Formal national and EU engagements to gather inputs on the CT design, ensuring that the endpoints will be accepted by payers,
- Early access schemes to increase the early experience with new therapies, better understand their place in therapy, and generate additional evidence on their benefits which may not have been captured in the clinical program
- Innovative agreements allowing a partnership with authorities who are uncertain on the long-term benefits of a drug but are open to finding ways to cover the treatment at reduced risk
- RWE to help support regulatory and market access, through value quantification (PROs, burden of disease, clinical and economic value, willingness to pay) to substantiate the added benefits of bringing a new treatment into real world practice.

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WP July 2020 v1 070920