OHE

The Importance of Diversity of Supply in Rare Disease Markets

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Executive Summary

The challenges surrounding the research and development (R&D) and later commercialisation of medicines for rare diseases (RDs) are well known. While policies and incentives have been introduced at regulatory and reimbursement levels to address these challenges, markets for RD medicines are still characterised by a lack of competition and few treatment alternatives for patients.

Access to — and the availability of — effective treatments is crucial for positive health outcomes, patient quality of life, and an efficient health system. A significant risk to this, however, is the occurrence of medicine shortages, which have become more frequent in recent years and can have severe consequences for patients. This risk of shortages can be amplified by certain market characteristics, such as limited competition and a lack of treatment alternatives, as well as procurement mechanisms that promote a single supplier (e.g., tenders). These market characteristics are typical in RD medicine markets, given their small patient populations and low financial incentives for innovators to invest and compete. This results in limited treatment options for patients — sometimes even when appropriate medicines have received regulatory approval. Additionally, because RDs generally are chronic and seriously debilitating, people with RDs are likely to acutely feel the impacts of medicine shortages, especially when treatment alternatives are not available.

Supplier diversity provides additional resiliency to the healthcare system and can be an enabler for pharmaceutical innovation.

Supplier diversity improves supply and healthcare system resilience, helping to mitigate the impact of medicine shortages. Other innovators supplying in the same market could help cover a shortfall in production or provide therapeutic alternatives, which could restore optimal healthcare provision in a shorter period of time, ultimately reducing the likelihood of serious harm to patients and health systems.

Supplier diversity can also be associated with iterative pharmaceutical innovation in well-functioning medicine markets. Iterative innovation provides access to multiple therapies of different classes while it expands in-class competition and access to innovation. This can generate knowledge spillover; help identify remaining unmet needs for patients and provide sufficient return on investment — three elements that jointly drive investment in future innovation towards areas of the highest value to society.

Our policy analysis found that there is mixed progress and recognition of this value.

There is generally a recognition that medicine shortages are a critical issue in relevant non-RD-specific policies and strategies. However, this is not currently reflected in RD medicine policies. Indeed, our review found no guidance aimed specifically at preventing RD medicine shortages and/or improving supplier diversity in RD medicine markets in order to enhance supply resilience. This is despite the additional risk and potential impact associated with shortages of these medicines.

Value-based assessments that reward the value added by innovation and incentives for orphan medicinal product innovators are necessary to incentivise future innovation in the areas of highest value and unmet need. However, doing so should not preclude improving supplier diversity and healthcare system resilience by promoting access to approved and valuable further treatment options for patients.

Furthermore, procurement mechanisms and policy should also not function as a barrier to the co-existence of multiple suppliers. They should be designed (within the existing legal framework) in a way that promotes market entry and competition between multiple suppliers of equivalent or similar therapeutic alternatives. For example, tendering mechanisms should aim to avoid using a winner-takes-all design and promote approaches with multiple winners and suppliers.

Policymakers at all levels need to ensure policies are consistent and well-aligned.

High-level policy and national strategies can promote sustainable and resilient medicine supplies. There is still room to expand RD policies to prioritise medicine shortage mitigation, supplier diversity, and supply resilience.

HTA, pricing and reimbursement, and procurement policies can help reduce barriers to the availability of medicines and supplier diversity. Value-based assessment of innovation must continue being the core element, complemented by recognition of the value added by supplier diversity and supply resilience.

Procurement mechanisms can adopt more targeted and inclusive decision rules to promote supplier diversity and healthcare resilience against the risk of shortages.

1. Introduction

The challenges surrounding the research and development (R&D) and later commercialisation of medicines for rare diseases (RDs) are well known. The small size of patient populations and the lack of effective treatments make the development of medicines for RDs complex and financially risky (Berdud et al., 2020). RD medicines also face challenges in the generation of evidence for both regulatory approval and health technology assessment (HTA). This is often due to challenges in patient recruitment or the lack of validated endpoints, among other difficulties (Annemans et al., 2017; Drummond et al., 2007).

Many policies and incentives have been introduced at regulatory and reimbursement levels to help address these challenges. For example, the introduction in the EU of the Regulation on Orphan Medicinal Products (OMP), and the Orphan Drug Act in the US, recognized the need for effective regulatory incentives to promote R&D and the marketing of new medicines for RDs. Both provide orphan-designated medicines enhanced protection with extended market exclusivity and increased regulatory support for clinical development plans. In addition, national RD strategies increasingly include explicit actions to improve access to RD medicines, along with tailored considerations in HTA and reimbursement at the country level. All these measures have proven essential for increasing the development and approval of new medicines for RDs (Neez et al., 2020; Berdud et al., 2020) while also acknowledging the inherent challenges in developing such treatments. However, incentives based on enhanced protection–which by design prohibits competitors marketing new therapies with the same active ingredient–should not deter the entry of other innovative therapies that may benefit the same group of patients (brand competition). Yet, in practice, RD markets still face limited competition and treatment options, often even after market exclusivity expires (Berdud et al., 2020). Resolving these issues requires promoting the development of new therapies and improving access to existing RD treatments through greater competition among innovative medicines.

A robust and resilient supply that enables optimal availability and procurement of life-saving medicines is an essential component of a well-functioning pharmaceutical market that can meet the demands of patients and health systems. Our previous research on the causes and consequences of medicine shortages –defined as situations when the total supply of all approved clinically interchangeable medicinal therapies is insufficient to meet user-level demand– demonstrates the risks and profound consequences when this supply breaks down (Napier et al., 2024; Napier, Berdud and Cole, 2024). Many factors contribute to medicine shortages, including supply issues, unanticipated demand increases, tendering, and price erosion (Napier et al., 2024). Factors driving medicine shortages can be short- or long-term. Long-term drivers, like procurement mechanisms (e.g., tenders), create chronic risks, while short-term factors, such as natural disasters damaging facilities, cause acute shortages. Long-term drivers may lead to recurring short-term effects; for instance, poorly designed tenders can result in repeated supply disruptions over time. The risk of a shortage is higher in concentrated medicine markets (with few suppliers) or those characterised by a single supplier (Napier et al., 2024). Insufficient diversity of suppliers and market concentration in medicine markets for RDs are important factors to consider in terms of the risks of medicine shortages. Moreover, market concentration appears to be related to the level of difficulty associated with resolving shortages. This is because when a manufacturer suffers a supply issue, it is more difficult for the manufacturers of treatment alternatives to cover the supply shortfall, likely resulting in a greater impact of the shortage.

The impact is even more pronounced in cases where there are no equivalent or similar therapeutic alternatives available. In these cases, the inability to switch patients to treatment alternatives of similar effectiveness leads to worse health outcomes for those patients and results in significant negative health impacts (Napier, Berdud and Cole, 2024). The fact that RDs are likely to be chronic

and seriously debilitating (EMA, 2024) means that people with RDs could more acutely feel the impacts of medicine shortages when effective alternatives are unavailable, as they may face more serious and life-long consequences from treatment discontinuation.

Beyond supplier diversity, there are many other factors contributing to higher rates of a shortage in certain therapy areas, several of which are relevant to RDs. For example, the development of new innovative biologics that more precisely target RDs (often genetic in nature) is becoming more common. The impact of shortages may be relatively higher in biologic markets because the manufacturing process is complex and specialised, involving multiple stages that make the final product more susceptible to quality issues affecting the safety and the effectiveness of the medicine (Dranitsaris et al., 2017; Ramanan and Grampp, 2014). Viral contamination, for example, has been reported as a cause of shortage for biologics for RDs (Trafton, 2020; Barone et al., 2020; Ramanan and Grampp, 2014). Manufacturing complexity and specificity also contribute to rigidities in supply, making it more difficult for manufacturers of a biologic medicine in shortage to resume production, and for alternative suppliers to adapt production to meet the increased demand (Mica, Mutomba and Green, 2013; Grampp and Ramanan, 2013).

Even when new treatment options receive regulatory approval, procurement mechanisms and reimbursement policies can also play an important role in shaping medicine markets, either encouraging or discouraging supplier diversity and competition. For example, the use of single-winner tenders can lead to highly concentrated markets with single or few suppliers (Dranitsaris et al., 2017), or promote monopoly-like conditions (Barrenho et al., 2023), which increases the risk of experiencing supply issues. Some HTA and reimbursement policies can also affect the diversity of suppliers in medicine markets, for example those that consider only therapeutic added value and do not place any worth on equivalent treatment alternatives (Nijhuis, Guan and Tewary, 2019). In both cases, the consequences are amplified in the context of RDs, where the patient populations are small and there is a baseline lack of incentives for innovators to innovate and to enter these markets.

We hypothesise that many of the issues described could be mitigated through the diversification of suppliers, particularly in RD markets. Supplier diversity is characterised by multiple manufacturers being in the market in a therapeutic area, creating additional resiliency in the supply chain and the healthcare system. Multiple manufacturers in a market also increases competition and may improve payers' affordability and the sustainability of healthcare systems (Roediger et al., 2019; Berdud et al., 2018). On-patent competition among innovative medicines and supplier diversity enhances societal value while continuing to reward pharmaceutical R&D.

This study aims to characterise the risks associated with single suppliers in the context of medicine markets for RDs and how current procurement, as well as pricing and reimbursement mechanisms, may be contributing to the problem. We outline how supplier diversity could help mitigate some of the risks and lead to potential wider benefits. We also explore current trends and potential strategies for integrating features into procurement and reimbursement mechanisms that promote supplier diversity in markets. These are primarily explored through a targeted literature review and evidenced by a series of real-world case studies.

We also undertake a policy review to assess key national and EU-level policy and legislative documents in the following three areas: i) National and EU-level plans for RDs, ii) National HTA and reimbursement processes for medicines for RDs and orphan medicines, iii) National and EU-level policies promoting and/or discouraging diversity of supply. This is to assess whether the mechanisms and aims of the policies are aligned with one another, both at a national and EU-level.

The report is structured as follows. In section 2, we set out the methods underlying the targeted literature review, the case studies, and the policy review. In section 3, we highlight the risks of single-supplier medicine markets, and the benefits associated with supplier diversity. In section 4, we review and assess the policy landscape at EU-level and for a set of selected countries. Section 5 provides a discussion of the findings, before concluding remarks and recommendations are offered in section 6.

2.Methods

2.1. Literature review

We conducted a rapid evidence assessment to explore the potential benefits of supplier diversity in the market for RD medicines, as well as the potential risks associated with single-supplier markets.

We developed a search strategy (outlined in the following sub-section) to perform a search in PubMed. We also revisited the literature identified in our previous research relating to the causes and consequences of medicine shortages (Napier, Berdud and Cole, 2024; Napier et al., 2024). Furthermore, we performed a snowballing (citation chaining) search, whereby we identified further papers from the references of the included papers to identify further relevant material.

2.1.1. Search strategy

Table 1 below outlines the search strategy we developed, and the number of results associated with each search, correct as of 23rd October 2024. The aim was to identify papers across three different themes:

- The risks associated with single-supplier markets and tendering in terms of medicine shortages and risk to supply.
- The benefits of healthy competition (multiple suppliers) in markets for RD medicines
- The benefits of on-patent/in-class competition

TABLE 1 PUBMED SEARCH STRATEGY

Search	Query	Results
#1	"Drug Industry"[MeSH Terms] OR "pharma*"[Title/Abstract] OR "drug industr*"[Title/Abstract] OR "pharma*"[Title/Abstract] OR "drug"[Title/Abstract] OR "medicine*"[Title/Abstract]	3,004.741
#2	"competition"[Title/Abstract] OR "contestable market*"[Title/Abstract] OR "market efficiency"[Title/Abstract] OR "allocative efficiency"[Title/Abstract] OR "competition polic*"[Title/Abstract] OR "monopoly"[Title/Abstract] OR "concentrated"[Title/Abstract]	203,527
#3	"rare disease*"[Title/Abstract] OR "orphan drug*"[Title/Abstract] OR "orphan medicinal products"[Title/Abstract]	37,870
#4	(#3) AND (#2)	125
#5	"on-patent competition"[Title/Abstract] OR "class competition"[Title/Abstract] OR "brand competition"[Title/Abstract] OR "follow-on drug"[Title/Abstract]	81
#6	"tender*"[Title/Abstract] OR "single suppl*"[Title/Abstract]	30,987

#7	"shortage*"[Title/Abstract] OR "supply issue*"[Title/Abstract] OR "unavailab*"[Title/Abstract] OR "supply disruption*"[Title/Abstract]	81,029
#8	(#7) AND (#6)	70
#9	((#4) OR (#5)) OR (#8)	275
#10	(#1) AND (#9)	120
#11	"clinical trials as topic"[MeSH Terms]	398,538
#12	(#10) NOT (#11)	111
#13	(#10) NOT (#11) Filters: in the last 10 years, English	75

2.1.2. Inclusion and exclusion criteria

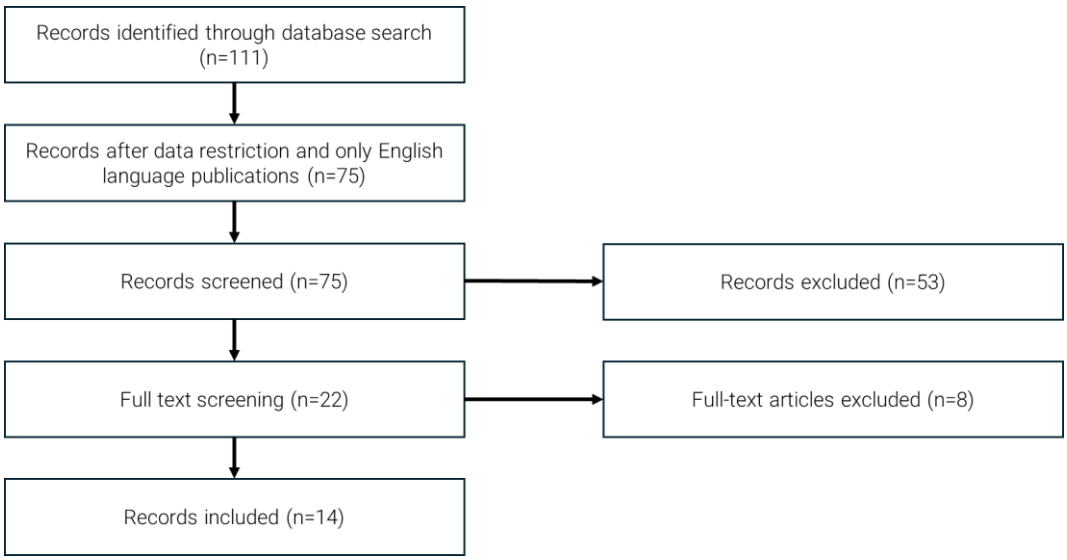
The search results were screened for relevance with a title and abstract review, followed by a full-text review. Relevance was assessed based on a discussion of the risks associated with single-supplier or concentrated markets (e.g. medicine shortages), the added value of supplier diversity, and the causes of single-supplier or concentrated markets.

The exclusion criteria are outlined below:

- Medicine shortages due to causes beyond a single-supplier or concentrated markets
- Non-English language
- Studies published before October 2014 (10-year date restriction on publication)
- Studies not relevant or related to either single-supplier markets or supplier diversity

Figure 1 below shows the process of filtering leading to the inclusion of 14 papers from the PubMed database search. An additional 25 papers were identified through hand-searching the reference list of the studies, and revisiting the academic literature identified in our previous research on medicine shortages (Napier et al., 2024; Napier, Berdud and Cole, 2024).

FIGURE 1 PRISMA DIAGRAM



2.2. Case studies

A set of case studies were selected to provide supporting evidence and illustration of the identified risks of having a single supplier and the added value of supplier diversity, with a focus on medicines targeting RDs.

In searching for case studies relating to the risk of single-supplier situations, we firstly focused on the risk of a medicine shortage and identified well-documented medicine shortages in the European Union that lasted longer than 6 months for acute therapies and over a year for chronic therapies.

Secondly, based on the results of the literature review, we performed a targeted search for case studies to document risks associated with concentrated markets and the role of tendering in promoting single-supplier markets.

Finally, further case studies were identified to explore the impact of multiple suppliers of innovative medicines, either within the same class or across different classes of therapies developed and approved for the same disease.

Table 2 provides a summary of all case studies selected using the three approaches.

TABLE 2 SUMMARY OF CASE STUDIES

Case study name	Type	Description
Cerezyme (imiglucerase)	Shortage caused by viral contamination	• Shortage without availability of alternative product. • There were attempts to facilitate early access of competitor products . • Patients were required to reduce dosing amid shortage. • Negative impact to patients' health documented.
Fabrazyme (agalsidase beta)	Shortage caused by viral contamination	• Shortage with one alternative product available for certain geographical regions. • Patients were required to switch therapy (if alternative product was available and switch was allowed) or reduce dosing. • Impact on patient health documented.
Cinryze (C1 inhibitor, human)	Shortage caused by production issues at manufacturing plant	• Shortage with alternative products available. • No wider impact for patients as alternative treatment options were available. • Alternative products also demonstrated technological advantage (recombinant technology vs plasma derived) that can help mitigate shortages.
IV infusion products	Concentrated market	• Market with various suppliers but local market concentration.

		• Shortages due to manufacturing issues occurred over the recent years. • Most recently one shortage was caused by a manufacturing plant that was hit by a hurricane. • The affected manufacturer supplied up to 60% of the supply in some affected markets.
Generic medicine market	Use of tendering and concentrated markets	• Markets characterised by the competition of multiple suppliers. • Use of cost-containment policies and procurement mechanisms, e.g. tenders, lead to low supplier diversity and monopoly-like conditions in some markets. • This dynamic increased generic market risk of shortages and health system vulnerability.
Haemophilia	Benefits of iterative innovation and supplier diversity	• Area where continued investment in R&D led to the development of multiple therapy classes and treatments. • High penetration of innovation characterised by a wide adoption and uptake of innovation. • Evidenced spill-over effects. • Area with remaining unmet need. • Expanded access to innovation globally with positive impact on patients' health and quality of life.
Duchenne Muscular Dystrophy	Benefits of supplier diversity	• RD with remaining unmet need requiring patient-centric approach with multiple therapeutic options. • A disease where iterative innovation has contributed to development of new medicines and patient outcomes improvement. • Area where knowledge spillovers have contributed to the development of innovative therapies. • A disease where access to multiple treatment options is still immature and lack of available alternatives can be an issue.

2.3 Policy review

In order to identify policy-level actions and strategies that relate to supplier diversity for RD medicines, we performed a targeted review of key national and EU-level policy and legislative documents in the following three areas:

- National and EU-level plans for RDs
- National HTA and reimbursement processes for RDs and orphan medicines
- National and EU-level policies promoting and/or discouraging diversity of supply.

The focus of the policy review was the EU. We targeted EU-level policies and plans for the three relevant areas and a set of selected member states (MS): France, Germany, Belgium, the Netherlands, and Denmark. The United Kingdom (in Europe but not a member of the EU), Canada and Australia have also been added to the selection to provide an international context and allow relevant comparisons. Selection of the three non-EU countries was based on the national health care, health system and HTA similarities.

3. The importance of supplier diversity

3.1. The risk of having a single supplier

3.1.1. Medicine shortages and single suppliers

Medicine shortages pose a serious risk to the industry, health systems, and most importantly patients. In recent years, medicine shortages have risen in frequency across the US, EU, and Canada (Napier et al., 2024). Many factors contribute to medicine shortages, including but not limited to supply issues, unanticipated demand increases, tendering, and price erosion (Napier et al., 2024); often these are multi-factorial and interlinked. Our analysis also highlighted that medicine shortages often occur in highly concentrated markets, namely those with one or a small number of suppliers. Sometimes, the factors driving shortages also contribute to market concentration. For instance, price erosion results in low prices and margins (Napier et al., 2024), which may force manufacturers out of the market, increasing market concentration and causing supply issues if the remaining manufacturers cannot meet the demand.

Arguably the highest risk associated with medicine markets served by a single supplier is the risk of shortage. In the event of a shortage with a single supplier, patients cannot be switched to an equivalent alternative therapy, and it is patients who bear the consequences of the disrupted supply.

This has been documented with a hypothetical case of a trastuzumab shortage where a small proportion of patients unable to switch to an equivalent therapy leads to health loss for patients (Napier, Berdud and Cole, 2024). The patients who were switched to the previous standard of care lost out on the improved (quality-adjusted life year (QALY)) health outcomes provided by trastuzumab in this indication, which was projected to result in significant health losses.

The need to postpone treatment, reduce dosing, prioritise patients and/or switch them to inferior alternatives to mitigate impact, results in significant health losses to patients (Napier, Berdud and Cole, 2024; Miljković et al., 2019; De Weerdt et al., 2017).

Adverse events and mortality may increase during a medicine shortage, the most severe consequence of medicine shortages reported in the literature. However, the mortality impact depends on the disease severity and the therapeutical value of the treatment in shortage, making it difficult to establish accurate measures of this impact (Phuong et al., 2019).

Even though the cost of a shortage in single-supplier markets is likely to be most keenly felt by patients, the total cost is of a much wider scope, affecting payers' budgets via higher prices (ASPE, 2023; Hernandez et al., 2018; Miljković et al., 2019) and health system efficiency and resource use (Goldsack et al., 2014; Wiggins et al., 2014; Miljković et al., 2019).

Medicine markets for RDs are more vulnerable to risks of shortages. The small market size of orphan and RD medicines may increase the risk of shortages, with a lack of financial incentive to manufacture medicines of this type and compete in markets cited as reasons (Shukar et al., 2021; Mazer-Amirshahi et al., 2014).

Furthermore, those markets which are typically served by only one treatment option are characterized by a lack of physician and patient choice during a shortage (Jarosławski et al., 2017). An analysis by the Office of Health Economics of orphan medicinal products at the indication-level using EMA data of 2018 showed that fewer than 15% of the treatment indications had more than one innovative therapeutical option (still protected by market exclusivity). This proportion increases to 17% in indications where generic/biosimilar entry is enabled (Berdud et al., 2020).

Beyond the threshold of a disease being considered rare if it affects fewer than five in 10,000 (EMA, 2018), the EMA defines RDs as life-threatening or chronically debilitating conditions (EMA, 2024). The consequences of medicine shortages for these patients are therefore likely to be high (Musazzi, Di Giorgio and Minghetti, 2020), particularly for those diseases which are progressive in nature. Studies found that, for some conditions, once patients progress to a more severe stage of the disease they cannot be brought back to previous stages and health status, which means significant health loss and increased burden to the health system (Jarosławski et al., 2017). Several examples in Fabry Disease (Karaca et al., 2022), Pompe Disease (Tard et al., 2022) and Gaucher Disease (Machaczka et al., 2015; Deroma et al., 2012) document this impact risk of shortages in RDs.

Some patients in the COVID-19 pandemic missed out on two or more doses of enzyme replacement therapy for Fabry Disease, which led to a worsening of symptoms (Karaca et al., 2022). The complete discontinuation of the treatment can result in a rapid deterioration of a patient's organs and new Fabry manifestations. A similar effect was seen in patients with Pompe disease, again during the COVID-19 pandemic (Tard et al., 2022); data from the French Pompe Registry showed that the interruption of treatment, even for as little as a few months (mean 2.2 months), resulted in a significant deterioration in patients' motor and respiratory function. This reduced dosing or discontinuation of treatment can also occur as a result of a shortage.

Supply shortages of imiglucerase for treating Gaucher Disease have led to dose reduction or withdrawal of treatment (Deroma et al., 2012; Machaczka et al., 2015). In one study, the median reduction in the dose was 36%, and the results suggested that, even for a short period, the dose reduction led to a worsening in clinical biomarkers for patients with Gaucher Disease type 3 (Machaczka et al., 2015). Another study didn't show a significant change in laboratory parameters due to dose reduction; however, there was a worsening in the well-being and bone pain of some patients with Gaucher Disease type 1 (Deroma et al., 2012).

BOX 1: CEREZYME CASE STUDY

Gaucher disease is one of the most common lysosomal storage disorders caused by a deficiency in the enzyme glucocerebrosidase. It can be classified into three clinical subtypes, which have diverse symptoms and severity and affect the macrophage system or central nervous system (Zimran, Altarescu and Elstein, 2011; Hollak et al., 2010). Gaucher disease was the first lysosomal disorder to have a clinically effective enzyme replacement therapy. In 1994, the recombinant enzyme Cerezyme was approved for lifelong biweekly intravenous administration (Hollak et al., 2010). It was the only approved product with a single supplier until the approval of the first alternative recombinant therapy, Vpriv, in 2010 (Cox, 2013; Dussen et al., 2012). In 2009, production of Cerezyme was halted due to viral contamination at the manufacturing facility, reducing global supply to 20% and causing a worldwide shortage exacerbated by further production issues (Hollak et al., 2010).

In a shortage, the lack of effective treatment alternatives can increase the risk to patients of health loss, but this can be mitigated when alternatives are available. With no alternative enzyme replacement therapy available, medicines were rationed, with the most severe patients receiving treatment, while the less severe patients received reduced doses, or no treatment at all (Hollak et al., 2010; Zimran, Altarescu and Elstein, 2011; Dussen et al., 2012). Withdrawal of enzyme replacement treatment led to clinical deterioration, including symptoms such as fatigue, bone infarction, bone pain, or hepatomegaly (Zimran, Altarescu and Elstein, 2011; Stirnemann et al., 2015). Reduced doses also affected biomarkers and results from laboratory tests (Machaczka et al., 2015; Deroma et al., 2012; Stirnemann et al., 2015). However, short-term reduction or withdrawal was considered unlikely to lead to irreversible complications (Zimran, Altarescu and Elstein, 2011).

The FDA and the EMA reached out to manufacturers of potential alternative enzyme replacement therapies in late clinical development, including velaglucerase alfa and taliglucerase alfa (Hollak et al., 2010). In 2010, Vpriv received marketing authorization, allowing patients to switch to this effective alternative enzyme replacement therapy with similar safety profile (Dussen et al., 2012). Today, there are more competitors in the global market for enzyme replacement therapy in Gaucher including Vpriv and Elelyso. This competition may mitigate manufacturing and shortage issues in the future.

This case study exemplifies that, **the lack of available alternative treatments made patients with Gaucher disease pay the cost of Cerezyme shortage with clinical deterioration**. When the use of an alternative was available, patients who switched to the alternative did not deteriorate. **Supplier diversity and availability of treatment options enables increased treatment security to health care systems and patients suffering from rare diseases.**

Several studies have explored risks of medicine shortages in relation to market concentration more generally, finding that the more concentrated the market is for the product, the greater the probability that competitors can't meet patient demand when a shortage occurs (Musazzi, Di Giorgio and Minghetti, 2020; Bogaert et al., 2015).

The association between market concentration and shortage risk is seen across multiple markets (the US, Canada, and Europe). Indeed, in the US market for antineoplastic medicines, an inverse correlation between the number of suppliers and shortage occurrence has been observed (Parsons et al., 2016). In addition, a retrospective cohort study in Canada identified that markets characterised by a single generic manufacturer had a higher likelihood of being in shortage (Zhang et al., 2020).

The availability of alternative treatments could ensure the continuity of care for patients; the lower the number of alternatives, the higher the potential impact on patients (Musazzi, Di Giorgio and Minghetti, 2020). However, even when therapeutic alternatives exist in a market, if those associated

with low market shares have to cover the supply shortfall of the market lead, then they are unlikely to be able to meet patient demand (Musazzi, Di Giorgio and Minghetti, 2020), due to difficulties in scaling production. A more even distribution of the market share, characteristic of true competition, would help mitigate this risk in case of a shortage occurring because a peak demand or a supply disruption of any of the competitors.

Overall, there are significant risks associated with single-supplier markets, primarily as a result of both the increased likelihood and impact of medicine shortages. These risks are compounded and worsened when experienced in RDs or essential medicines shortages. The case study below, exploring the shortage of Fabrazyme, illustrate a real-world example of this risk and resulting impact.

BOX 2: FABRAZYME CASE STUDY

Fabry disease is a lysosomal storage disorder caused by a deficiency in the enzyme α-galactosidase A. The disease affects multiple organs including the heart, kidneys, and nervous system, leading to a wide range of symptoms depending on the exact genotype. Fabrazyme, a recombinant enzyme replacement therapy, was the first therapy for the disease introduced in 2001 (Oder, Müntze and Nordbeck, 2021). In 2009, the production of Fabrazyme was halted due to viral contamination at the manufacturing facility, reducing global supply to 30% and causing a worldwide shortage exacerbated by further production issues (Smid et al., 2011; Liu, 2015; Linthorst et al., 2011). In the USA, full stock was restored in 2012 (Pharmavoice 2024).

In a shortage, the lack of effective treatment alternatives can increase the risk to patients of health loss, but this can be mitigated when alternatives are available. In the United States, Fabrazyme was the only available medicine for Fabry disease when it went into shortage. In an attempt to secure treatment options for Fabry disease patients, several legal discussions ensued and the FDA permitted limited "compassionate use" imports of a similar product from Canada (Liu, 2015; Nature Medicine Editorial, 2011). The shortage of Fabrazyme caused medicines rationing, with the most severe patients receiving treatment and reduced doses for less severe patients, or no treatment at all. Approximately 80% of patients went without medication for several months, leading to increased pain, fatigue, and one reported death (Liu, 2015). Reducing doses also increased pain attacks, chronic pain, gastrointestinal pain, and diarrhoea (Warnock and Mauer, 2014; Weidemann et al., 2014).

In other areas of the world, an alternative enzyme replacement therapy called Replagal, which had a different dosing regimen but similar clinical efficacy, was available (Europe, Canada, South America, Asia, and Australia) (Mehta, 2015). Patients in these countries could switch to Replagal, which in principle was well tolerated and maintained stable clinical conditions (Pisani et al., 2017). However, most recent studies have indicated a potential risk for decreased renal function after switching to Replagal, impacting negatively on patients health warranting further investigation (Riccio et al., 2023).

Today, there are more products in the global market, including the US (Oder, Müntze and Nordbeck, 2021; Vinluan, 2023; Liu, 2018), which means iterative innovation and competition, which can help mitigate manufacturing and shortage issues in the future.

The Fabrazyme shortage case shows that lack of alternative treatments is a risk for patients' health in markets for rare diseases, which are more often characterised by single suppliers. **This risk intensifies when the existing therapy is a biologic medicine** as the risk of supply issues is higher e.g., contamination. **Supplier diversity can mitigate and remove most of these risks faced by patients suffering from rare diseases.**

3.1.2. Single supplier tendering

Policies relating to procurement, pricing, and reimbursement can result in markets being served by a single supplier in the long-term, which could amplify the risk of a medicine shortage as described in section 3.1.1. For example, many of the studies included in the literature review discuss and describe how sole-supplier tendering can be a risk for medicine shortages (Dranitsaris et al., 2017; Biedermann, 2023; De Weerdt et al., 2015; Ryan, 2021; Németh et al., 2023; Maniadakis et al., 2018; Vogler et al., 2017).

Tendering is a procurement mechanism performed by public or private healthcare institutions to purchase medicines. Competitive bidding is performed for a particular contract to supply medicines. Tendering has been seen as an effective mechanism for selecting the most cost-efficient supplier and achieving short-term savings to pharmaceutical costs (Dranitsaris et al., 2017; Maniadakis et al., 2018; Vogler et al., 2017).

However, single-supplier tendering can impact the certainty of supply, have long-term distorting impacts on markets, and increase the risk and impact of medicine shortages. These negative impacts recur over time while the tendering mechanism continues driving the market structure, creating a long-term risk of shortage. The risk of medicine shortages described here also applies to highly concentrated markets or those with a single supplier as the increased risk of shortage is due in large part to the dependence on a single supplier (Dranitsaris et al., 2017).

BOX 3: INTRAVENOUS INFUSION PRODUCTS CASE STUDY

Intravenous fluids are one of the most common interventions in medicine, used for resuscitation, replacement, maintenance, and drug dilution (Malbrain et al., 2020). Despite their simple formulation, the manufacturing process is complex, requiring high quantities and strict sterility (Mazer-Amirshahi and Fox, 2018).

Concentrated markets with an overreliance on specific suppliers can increase the risk of drug shortages, impacting patient care and adjacent industries. Although the IV fluids market includes various suppliers (Coherent Market Insights, 2024), there is a significant dependence on a few major suppliers in national markets (Mazer-Amirshahi and Fox, 2018; NOS Nieuws, 2024; Chest, 2024). This dependency increases the risk of shortages due to manufacturing issues, with competitors struggling to compensate for supply gaps (Mazer-Amirshahi and Fox, 2018). Recently, IV fluid shortages have been reported following the disruption of a manufacturing facility in North Carolina due to a hurricane, affecting countries like the USA (Reuters, 2024; Southwick, 2024; Chest, 2024) and the Netherlands (College ter Beoordeling van Geneesmiddelen, 2024; Gaalen, 2024; NOS Nieuws, 2024). This manufacturer supplies about 60% of the IV fluids in the US and Dutch markets, prompting national regulators like the FDA and MEB to seek alternative supplies (Chest, 2024; NOS Nieuws, 2024; Gaalen, 2024).

Shortages can impact patient care in various ways, including delays in surgery, medication errors, and microbial contamination (Mazer-Amirshahi and Fox, 2018; Mishra and Santhosh, 2024). Additionally, the delay or cancellation of elective surgeries due to shortages can negatively affect related industries, such as the medical device sector (Mishra and Santhosh, 2024). Furthermore, shortages of IV saline in the USA may have impacted the price of the product, with the wholesale price doubling between 2014 and 2018 (Napier, Berdud and Cole, 2024). This can be partly attributed to the occurrences of shortages in that period.

This case study highlights the importance of having multiple suppliers to avoid concentrated markets and reduce the risk of shortages.

If the supplier suffers production issues, it is very difficult for this to be mitigated by other manufacturers who did not win the tender (Biedermann, 2023; De Weerdt et al., 2015), as it can take approximately 4-6 months to plan and execute production (De Weerdt et al., 2015). This could be worse when the medicines are associated with a complex manufacturing process, such as biological therapies.

The downward pressure on prices may also impact dynamic efficiency in the market (Maniadakis et al., 2018), due to lower incentives for pharmaceutical investment and therefore slower development of innovations (Dranitsaris et al., 2017). This could also lead to the exit of competitors from the market, and in the long run, this erosion of competition could potentially lead to higher prices (Dranitsaris et al., 2017) as a consequence of the resulting lack of competitive pressure to offer a cost-efficient price.

Furthermore, there is also a patient safety concern connected to sole-supplier tendering. A study explored the incidents caused by a medicine change as a result of either tendering or a medicine shortage reported in the Danish Patient Safety Database (DPSD) (Poulsen et al., 2019). They identified 88 incidents (between January 2011 and March 2014) relating to adverse events. The main reasons for the incidents were: prescribing errors, incorrect dosage being dispensed or administered, and delayed/omitted treatment.

In addition, when price is the only award criterion of a tender, factors relating to the product value can be overlooked (Maniadakis et al., 2018), ultimately impacting patients. For example, the change from one product to another in a tender could lead to patients requiring an adaptation. This could involve switching from an oral-based medicine that can be taken at home to a hospital-infused product which may lead to a greater caregiver burden and potentially impact patients' quality of life.

Overall, the focus on short-term pharmaceutical savings when selecting suppliers for tenders can have distorting effects on the markets and expose the supply chain to additional vulnerabilities. This is due to the driving out of competition, exposing the market to a risk of medicine shortages, since there are no alternative suppliers to cover a shortfall in supply if a shortage were to occur. However, good tendering practices can help mitigate these potential issues. This could include the promotion of multiple supplier tenders and a consideration of factors beyond just price, for example, supply reliability. Furthermore, we propose that there should be opportunities and incentives for alternative treatment therapies and an assessment of the impact on patients and their caregivers of any treatment switching that may occur due to tendering.

BOX 4: GENERIC MEDICINE MARKET CASE STUDY

A well-functioning generic medicine market should ensure availability, affordability, and sustainability for patients, health systems, and innovators. Underpinning this should be a market characterised by several suppliers, ensuring supply chain resiliency and price competition.

Generic medicines are a core element of health systems across Europe. Approximately **70% of all medicines sold in Europe by volume are generics, but only account for 19% of the total market value** (Troein et al., 2024). In addition, generic molecules are increasingly becoming **available for more complex and chronic conditions and represent 60% of the top 10 therapeutic areas in Europe** (Troein et al., 2024).

However, the main focus of generic medicines isn't necessarily the value they provide and their integral role in health systems, but instead their cost-saving potential (Troein et al., 2024). In Europe, the generic market for medicines has been impacted heavily by cost-containment policies (Medicines for Europe, 2019), and has exposed these markets to the risk of medicine shortages.

These cost-containment measures are usually applied in the tendering of generic medicines. As described in section 3.2.1, **these practices can reduce market competition and increase these medicines' vulnerability to shortages**. This dynamic in the generic market is described below and in our previous research on the causes of drug shortages (Napier et al., 2024).

Prices in generic markets are being driven down, not through price competition, but instead through policies aimed at cost containment; for example, single-winner tenders. This leads to **suppliers exiting the market, or suppliers not entering the market in the first place** resulting in a continuation of a monopoly from the on-patent period (Medicines for Europe, 2019). This has been demonstrated to have occurred in Germany and Italy due to tendering (Medicines for Europe, 2019), and has been acknowledged by the WHO as an issue (WHO Regional Office for Europe, 2016).

This lack of supplier diversity, characterised by a lack of competition, is primarily impacting patients and health systems due to an increased vulnerability to and occurrence of medicine shortages. As described in 3.1.1 as well as in our previous research into the cost of drug shortages (Napier et al., 2024), these can have severe consequences for patients and health systems.

Furthermore, in the long term, **cost containment policies can lead to distorting effects**, particularly if competitors lack sufficient incentives to enter the market after the period of exclusivity. For example, there may be no incentive for the supplier to offer a cost-efficient price, due to the erosion of competition, leading potentially to higher prices.

This trade-off between pharmaceutical savings through cost-containment policies, and the risk and impact of medicine shortages combined with the other impacts described must be fully considered. A balance needs to be found in the development of procurement policies to ensure there is healthy competition and patient access to generic medicines (Medicines for Europe, 2019).

3.2. The added value of supplier diversity

3.2.1. Benefits of iterative innovation

Innovation is an iterative process and a collective societal effort where discoveries and the development of new health technologies build upon prior advances and knowledge. Innovation is thereby directed towards areas of unmet need, where there is the highest value delivered to patients and health systems, and correspondingly the highest commercial return to innovators (Henderson et al., 2024; Hofmann et al., 2021; Lakdawalla, 2018).

Developing innovation is a staged and cumulative process. When a new innovation (e.g., a first-in-class medicine) addresses an area of unmet medical need, the target for improvement for the next innovation is set; the remaining elements of unmet need can then be defined, highlighted and worked upon in the form of similar or alternative follow-on innovations (Henderson et al., 2024; Nijhuis, Guan and Tewary, 2019). This approach has the potential to deliver huge improvements to benefit patients, physicians, health care systems and payers (Nijhuis, Guan and Tewary, 2019).

Having multiple therapeutic alternatives – which may differ in therapeutic profile, adverse events, dosing schedule or delivery system – enables wide patient access to effective treatment. Enhanced physician choice allows them to optimise patient management, treating different patient subpopulations according to their clinical needs and response to or toleration of each existing option (Nijhuis, Guan and Tewary, 2019; Cohen and Kaitin, 2008; Wertheimer, Levy and O'Connor, 2001). Treatment choice also provides value to patients in the form of spill-over effects such as better day-to-day treatment experience, overall treatment convenience and improved adherence (Toumi and Rémuzat, 2017; Wertheimer, Levy and O'Connor, 2001).

For example, different Beta Blockers for the treatment of cardiovascular disease differ in their medicine interaction profiles, enabling different cohorts of patients to be treated optimally (Globerman and Lybecker, 2014). A similar case is oncology, where different patients respond to different treatment alternatives of the same class and therefore benefit from having multiple alternatives for treatment (Nijhuis, Guan and Tewary, 2019).

Additionally, a therapy class with multiple treatment alternatives provides insurance value for patients by reducing the risk of shortages. This is the value an individual derives purely from having access to health services or treatments, even if they do not currently use them. The hypothetical case of a statin shortage which resulted in no health losses to patients due to the ability to switch patients to other statin alternatives (Napier, Berdud and Cole, 2024) exemplifies the importance of treatment alternatives.

Adoption and uptake of innovation generates spillovers and defines the remaining unmet need, shaping the direction for innovation to keep progressing. It also provides return on investment which, combined with spillovers and defined unmet need drives the future investment in R&D to areas where the value of innovation to society is the highest (Henderson et al., 2024). This is highlighted in the haemophilia case study discussed in Box 5.

BOX 5: HAEMOPHILIA CASE STUDY

Haemophilia A and B are hereditary haemorrhagic disorders characterised by deficiency or dysfunction of coagulation protein factors VIII and IX, respectively (Peyvandi, Garagiola and Abbattista, 2023). Haemophilia A and B are both rare diseases with prevalences of 0.7 and 0.2 cases in 10,000 people respectively (Henderson et al., 2024). Patients with severe haemophilia experience recurrent spontaneous bleeds, often in the absence of trauma, impairing their quality of life (Franchini and Mannucci, 2017) and leading to haemophilic arthropathy characterised by chronic joint inflammation and deformity (Knobe and Berntorp, 2011).

In haemophilia, continued investment in R&D has led to the launch of several new treatments and innovations, each with unique benefits to patients. Multiple new treatments provide physicians and patients with treatment alternatives, meaning they can make treatment decisions based on their clinical needs, physical activity level, and lifestyle (Henderson et al., 2024). Haemophilia treatment experienced a massive improvement with the introduction of the plasma derived FVIII and FIX concentrates in the 70s. Since then, new treatment classes have followed, providing multiple treatment options within and across classes and huge health gains to patients, including longer life expectancy (Hassan et al., 2021; Mannucci, 2020). In particular, the emergence of recombinant coagulation FVIII and FIX factors have led to huge advances in the treatment of haemophilia due to their improved safety profile and availability (Schiavoni et al., 2019; Coppola et al., 2014). These have been followed by extended half-life FVIII and FIX factors (Ar, Balkan and Kavaklı, 2019) and therapeutics with alternative mechanisms of actions or different classes like mimetics (Mannucci, 2020), anti-TFPIs, and anti-Thrombins (Mancuso, Croteau and Klamroth, 2024), and gene therapies (Leebeek and Miesbach, 2021). Prophylaxis induced with clotting factor- concentrates (CFC) (e.g., recombinant FVIII and FIX factors, extended half-life (EHL) FVIII and FIX factors) is the current standard of care in haemophilia (Ozelo and Yamaguti-Hayakawa, 2022; Srivastava et al., 2020).

Adoption and uptake of available innovation, scientific spillovers and the remaining unmet need have been the drivers of the staged iterative innovation in haemophilia. Unmet need has driven the focus of treatment advances while R&D has leveraged scientific spillovers to address these gaps (Kusynová et al., 2022). In the case of the EHL VIII and IX factors, they replaced standard half-life (SHL) factors which required more frequent doses to maintain therapeutic levels, and reduced the treatment burden for patients (Henderson et al., 2024). Much of the knowledge that allowed EHL blood clotting factors to stay in circulation for much longer periods came from developing, adopting and testing the previous class of factors, the SHFL factors.

Availability of multiple CFCs has expanded access globally, improved the health of patients and mitigated the risk of shortages. Multiple CFC treatment options are available in US and EU currently (Ozelo and Yamaguti-Hayakawa, 2022; Lim, 2021). For EHL factor only, there are five licensed FVIII and three FIX in EU (Lim, 2021). The global use of EHL is increasing (Ozelo and Yamaguti-Hayakawa, 2022). EHL-FVIII factors and EHL-FIX factors are available in 23 and 18 countries respectively and humanitarian aid has distributed them to other 37 and 18 countries respectively (Ozelo and Yamaguti-Hayakawa, 2022; World Federation of Hemophilia, 2024). In Europe, almost all western European children have access to prophylaxis, with central Europe showing progress since 2009 and eastern European children still lacking access. Adults' access in Western Europe covers almost the entire patient population in need, with a growing proportion in central and eastern Europe (Noone et al., 2020). Globally, the engineering and manufacturing of clotting concentrates have led to widespread availability of EHL. The transitioning from SHL factors to EHL has contributed to the transformation of haemophilia from a disease of significant morbidity to a disease that allows affected individuals to live active lives (Trinchero, Sholzberg and Matino, 2020; Traore et al., 2014; Fukutake et al., 2023; Hernandez et al., 2021; Marijke van den Berg, 2016).

Finally, while access is expanded to more innovative effective treatments (emicizumab, inhibitors) and cures (gene therapies), expanded access to multiple EHL FVIII and FIX is achieving huge health gains in haemophilia globally (The Lancet Haematology, 2024). In the decades preceding the expansion of supply of clotting factors, and EHL factors, limited access to clotting factors was mainly due to difficulties producing sufficient amount of (plasma) products. Supply shortages led to switch treatment guidelines from prophylaxis (prevention) to episodic therapy, forcing patients to accept bleeding treatment instead of prevention. Nowadays, with an abundance of EHL products that guarantees prophylaxis, treatment prevention of bleeding is the norm, and living a normal life is now the goal of therapy for all patients worldwide (Marijke van den Berg, 2016).

In haemophilia, continued investment in R&D led to the development of numerous innovations in an iterated process. Adoption and uptake of innovation generated spillovers and defined remaining unmet need, shaping the direction for continuing innovation to keep progressing. **The emergence of recombinant clotting replacement factors and the availability of multiple treatment options within the therapeutic class of extended half-life factors, led haemophilia patients to widely access products while issues with shortages were addressed.** Prophylaxis and bleeding prevention becoming standard of care has enabled patients with haemophilia to live normal, active lives.

In RDs, this insurance value is still unlocked. In Europe, the proportion of RD indications with more than one treatment alternative available for human use is exceptionally limited (Berdud et al., 2020). The impact of shortages in patients suffering from RDs is significantly more severe as we have discussed previously.

Promoting access to multiple available treatments in RD indications is therefore a strategy to consider unlocking the insurance value of incremental innovation, and guarantee patients the best care, whilst the risks associated with a shortage are mitigated. This potential value has been previously exemplified by the Cerezyme case study in this report. The Duchene Muscular Dystrophy (DMD) case study below adds evidence supporting the case for supplier diversity in RDs.

BOX 6: DUCHENNE MUSCULAR DYSTROPHY CASE STUDY

DMD is a severe inherited form of muscular dystrophy, and the most common hereditary neuromuscular disease. It is caused by mutations in the dystrophin gene, which is responsible for keeping the muscle cells intact. Muscle weakness is the principal symptom, usually manifesting from around the age of four. The muscle weakness progresses leading to cardiac and orthopaedic complications. Mortality risk increases with age due to respiratory muscle weakness and cardiomyopathy, with life expectancy typically in the twenties (Venugopal and Pavlakis, 2024).

There remains significant unmet need in DMD, which requires a patient-centric approach with multiple therapeutic options by multiple suppliers. Given the diversity of DMD-causing genetic mutations, a one-size-fits-all approach may not be feasible. DMD is often regarded as a "pioneer disease" in the realm of medicine discovery, where multiple companies develop and supply experimental treatments and iterative innovation across different classes of medicines. The variety of therapeutic strategies, ranging from less to more targeted, that are currently available and in development by multiple suppliers, contributes to a more patient-centric and comprehensive therapeutic approach and the potential use of combination therapies in the future (Roberts, Wood and Davies, 2023; Mullard, 2024).

For corticosteroids iterative innovation improved patient outcomes and expanded the eligible patient population. Corticosteroids are the standard treatment for all DMD patients, but they offer limited clinical benefits and can cause severe side effects, including impacts on bone and growth (Roberts, Wood and Davies, 2023). Recently, vamorolone was introduced as a first-in-class anti-inflammatory steroid analogue introducing competition and iterative innovation (Roberts, Wood and Davies, 2023; Kourakis et al., 2021; European Medicines Agency, 2023). Vamorolone matches the clinical efficacy of traditional steroids but has a significantly improved safety profile, making it suitable for a broader patient population, including older patients. Vamorolone's development and commercialization involved an innovative public-private partnership model, which reduced R&D costs and development time (Farrell, 2024; ReveraGen BioPharma, 2024b). Additionally, it has potential for scientific spillover to other muscular dystrophies and other conditions including asthma, inflammatory bowel disease, rheumatoid arthritis, or multiple sclerosis (ReveraGen BioPharma, 2024a).

For exon-skipping therapies, early access to multiple products provides patient benefit, while future iterative innovation is expected to improve their therapeutic advantage. Exon skipping therapies have the potential to address 55% of DMD-causing mutations and 80% of DMD-causing deletions (Roberts, Wood and Davies, 2023). Four FDA-approved exon-skipping therapies target different DMD exons: eteplirsen (exon 51), golodirsen (exon 53), casimersen (exon 53), and viltolarsen (exon 45). These therapies offer diverse and overlapping medicine targets, expanding patient populations. They have been approved for early access in the US, demonstrating modest clinical efficacy and good safety, but are not yet approved in the EU (Bendicksen, Kesselheim and Rome, 2024; Roberts, Wood and Davies, 2023). Looking ahead, the pipeline of exon-skipping therapies is promising, with further products enhancing competition and potentially lowering high introductory prices over time (Bendicksen, Kesselheim and Rome, 2024). Additionally, iterative innovation is expected to advance medicine formulation and delivery technologies with the aim to improve pharmacodynamics and patient outcomes (Roberts, Wood and Davies, 2023). Knowledge spillover from DMD and spinal muscular atrophy could support further development in other genetic disease areas (Lim and Yokota, 2018).

The withdrawal of the stop codon readthrough therapy Translarna (ataluren) will affect patient management in the EU, where there are no alternative targeted therapies available. Ataluren is a stop codon readthrough therapy that received conditional marketing authorization to treat DMD patients with single nonsense mutations by the EMA in the EU, but was never approved by the FDA in the USA (Roberts, Wood and Davies, 2023). Although the approval was based on some promising preliminary clinical data, the EMA recently withdrew the license amid concerns about its clinical efficacy (European Medicines Agency, 2024). In the EU, Translarna has been the only available targeted therapy for DMD despite its concerns regarding its efficacy. A richer therapeutic ecosystem with multiple suppliers of effective targeted therapies would be beneficial for DMD patients in the EU in this situation. With the EMA currently reviewing the first gene therapy for DMD (Pharmabiz.com, 2024), the future implications of the Translarna withdrawal for DMD patients remain uncertain.

Knowledge spillover from other diseases leads to more radical innovation and the adoption of gene therapies in DMD. The first gene therapy for DMD received marketing authorization by the FDA (FDA, 2023), and is currently under review by the EMA (Pharmabiz.com, 2024). This gene therapy provides functional mini-dystrophin protein for DMD patients (Roberts, Wood and Davies, 2023), utilising similar medicinal technology to that used in approved therapies for spinal muscular atrophy (Zolgensma) and retinal dystrophies (Luxturna) (Roberts, Wood and Davies, 2023). Multiple companies are developing gene therapies for DMD, although safety concerns have led to some withdrawals of competitors in the field (bioneststst, 2022; Becker, 2024). Nonetheless, there is potential for product differentiation based on technology and genetic subtype (Clara Zachark, Andrew Parece, and Matthew Majewski, 2022).

The DMD case study illustrates a **disease area with multiple suppliers developing and providing experimental treatments**. This environment **fosters innovation, increases competition, enhances patient health, and drives scientific advancements not only in DMD, but also in other diseases**. Despite significant progress in the availability of medicines for a rare disease like DMD, there remains a substantial need for therapies with greater efficacy that can benefit a broader range of patients (Roberts, Wood and Davies, 2023). **Addressing these unmet needs is expected to further stimulate the R&D environment, attract more suppliers, and drive iterative innovation** (Henderson et al., 2024).

3.2.2. Benefits of in-class competition

In-class competition in pharmaceutical markets occurs when different treatments are competing for market share within a specific therapeutic class. Products could be differentiated based on their side effects, mechanism of delivery, or even their clinical benefits. This offers patients and clinicians the flexibility to optimise treatment based on individual needs: addressing side effects with suitable alternatives, enhancing adherence through different delivery mechanisms, and maximizing clinical benefit by selecting the option to which the patient responds best. This form of competition between innovative medicines is often overlooked in the health system and has the potential to provide benefits in terms of price competition and improving the sustainability of strained healthcare system budgets (Roediger et al., 2019). Indeed, a few studies identified in the literature review observed that in-class competition has improved price competition, leading to downward pressure on prices (Roediger et al., 2019; Dave, Hartzema and Kesselheim, 2017; Berdud et al., 2018).

Two of the studies explored in-class competition in the market for Hepatitis C, where benefits were also seen beyond price competition (Berdud et al., 2018; Roediger et al., 2019). The dynamics of competition in the market led to price reductions, making new medicines more affordable to health systems, as well as improving health outcomes (Berdud et al., 2018; Roediger et al., 2019).

Furthermore, the in-class competition was said to drive the development of new treatments that addressed the remaining unmet need for patients (Roediger et al., 2019; Berdud et al., 2018). This is because competition between innovators drove innovators towards addressing the unmet need, and therefore ultimately improved treatment outcomes, providing incremental improvements to achieving reimbursement approvals (Roediger et al., 2019).

This effect can be best observed in the country-level analysis that was performed. Those countries that encouraged market competition (Spain and Italy), meaning full access was provided to direct-acting antivirals and their prices negotiated, resulted in greater QALY gains (Berdud et al., 2018). This was in contrast to settings where restrictions were imposed to control expenditure on the treatments (e.g. the United Kingdom until 2016).

However, arguably in-class competition could provide a risk for innovators, beyond the R&D risk, due to the shorter economic life of the product, falling price, and reduced market share (Roediger et al., 2019). This can be mitigated by ensuring the right amount of value is captured by innovators to ensure they have sufficient incentives for innovation (Berdud et al., 2018); ensuring the correct balance between dynamic and static efficiency.

Some evidence in the literature suggests that on-patent competition doesn't always lead to improved price competition (OECD, 2023; Ellyson and Basu, 2021; Sarpatwari et al., 2019; Michaeli and Michaeli, 2024). However, some of these studies explored this effect in the US market for pharmaceuticals (Sarpatwari et al., 2021; Ellyson and Basu, 2021; Michaeli and Michaeli, 2024), and their findings may be a result of market dynamics specific to that setting.

The OECD report found that the empirical evidence in the literature was mixed and their analysis highlighted that there was no clear evidence of price competition (OECD, 2023). However, their analysis didn't account for confidential discounts, which are often overlooked, can be significant (Roediger et al., 2019) and in practice may be where the actual price competition is occurring. Another acknowledged limitation of their analysis is the fact that 5 of the 6 indications they considered were undergoing intrinsic expansion due to changes to clinical practice (OECD, 2023), impacting the ability to draw robust conclusions of the effect of in-class competition.

In theory, successive market entries should result in price competition, and this has been seen in practice. However, the system must be designed in a way that promotes on-patent competition while ensuring sufficient incentive for investment in R&D, balancing dynamic and static efficiency.

3.2.3. Multi-winner tenders, enhancing competition, and availability of 'follow-on' products

Policies relating to procurement, pricing, and reimbursement should be designed in a way that enables therapeutic competition. Well-designed multiple-winner tenders could provide the cost-saving benefits seen with single-winner tenders. This is while helping to ensure resilience in the supply chain and retaining choice for patients and physicians when the burden of switching treatments is high. Tenders of this type are used in some European countries, for example Spain, Germany, Austria, Greece, Hungary, Italy, Portugal, and the United Kingdom; however, there isn't a general framework to design these tenders (Németh et al., 2023).

Németh et al (2023) propose five core principles that must be part of a well-designed tender, including having multiple winners to avoid the evolution of a monopoly in the long run, and implementing guarantees to supply to mitigate against shortages. Furthermore, multiple-winner tenders can ensure long-term competitiveness in the market, helping to maintain price efficiency (Maniadakis et al., 2018). This is because, when tenders result in monopolies, there is no competition in the market. Consequently, due to the exit of competitors from the market, in the long run there

may be limited competitive pressure to offer the lowest price in a tender, harming allocative efficiency. In contrast, if there are competitors, they will compete on price which should be an important part of a tender decision, but not the only factor considered.

For example, to help create more supply certainty in the market, purchasers could invite tender bidders to offer multiple prices, whereby the higher price is associated with a guarantee to supply a given volume (Ryan, 2021). This gives the purchaser a choice between a lower price and supply guarantees, enabling them to trade-off these considerations. The risk of shortage driven by price erosion and low margins can this way be ameliorated, creating a more stable and valuable market for suppliers willing to guarantee certain volumes, while preserving competition.

The design of tenders needs to consider the type of medicine, such as medicines for RDs and biologics. Due to small patient populations and manufacturing complexities, participants in tenders for RD and biologics markets face significant challenges in starting and stopping production based on bid outcomes. This often forces losing suppliers to exit the market, reducing resilience and increasing the risk of shortages. The case for multiple-winner tenders in these markets is clear. For RD markets, having multiple suppliers could improve patient and physician choice, mitigate against patient impact if shortages occur, and stimulate competition in the market.

For biologics, the complex manufacturing processes associated with medicines of this type and the relatively high investment needed to produce these treatments, require additional consideration from payers. The ability to switch on-and-off production is much more difficult in comparison to small molecule markets.

Beyond tenders, the availability of therapeutic alternatives in markets can both benefit patients and help mitigate the impact of medicine shortages (Aronson and Green, 2020). They offer additional therapeutic benefits in part due to the additional patient and physician choice (Rai et al., 2023). Furthermore, the availability of therapeutic alternatives allows patients to switch to alternative treatment if a shortage occurs. In this scenario, it is of course very important to consider some of the potential safety issues that can arise from medicine changes (Poulsen et al., 2019; Aronson and Green, 2020).

As outlined in section 3.3.2, in-class competition can help generate price competition in the market. A wider spillover effect of this is that it could potentially enable improved global access to medicines as they enable increased affordability of medicines in lower-income settings due to these competitive pressures (Aronson and Green, 2020).

BOX 7: CINRYZE CASE STUDY

Hereditary angioedema (HAE) is a rare genetic disorder characterised by recurrent episodes of severe swelling that affects limbs, face, intestinal tract, and airways (Longhurst and Bork, 2019). It is caused by deficiency of C1 esterase inhibitor (C1-INH) that results in excessive levels of bradykinin which results in swelling and tissue inflammation (Fijen, Bork and Cohn, 2021; Longhurst and Bork, 2019). Airway swelling can cause laryngeal oedema which is potentially life-threatening. Incidence and prevalence of HAE has been estimated at around 1 case in 50,000 people worldwide (Cicardi et al., 2014). Therapy encompasses on-demand treatment (ODT) of acute attacks and short- and long-term prophylaxis (STP, LTP). Currently, there are multiple approved therapies available for ODT, STP and LTP (Fijen, Bork and Cohn, 2021; Caballero, 2021).

The risk of shortages in rare diseases is a real threat, which is challenging to resolve in the short-term. Cinryze is a plasma derived C1-INH replacement therapy approved by EMA for ODT, STP and LTP treatment of HAE in children and adults. In 2017, production issues at a contract manufacturing organisation (CMO) led to a Cinryze shortage. The issue emerged even though the manufacturer acquired manufacturing plants in a company buyout, as regulatory approvals to release batches of product manufactured in new plants took several months (Palmer, 2017). The shortage in the EU lasted for 23 months (EMA, 2020). Use of Cinryze for new patients or for on-demand treatment was stopped, while patients on prophylaxis treatment with Cinryze were advised to continue treatment. The shortage affected Austria, Denmark, France, Germany, Ireland, Italy, Spain, Sweden, and the United Kingdom (pre-Brexit). Iceland, and Norway (EMA, 2020).

Diversity of supply is key in rare diseases to optimise treatment to patients, mitigate impact of medicine shortages in patients and health systems, and enable the benefits from competition and functioning markets. There are multiple treatment options for HAE classified into five different classes: antiplasmins, C1-INH synthetisers, C1-INH replacement therapies, B2R blockers and Kallikrein inhibitors (Caballero, 2021). More than one treatment option is available within all classes, except B2R blockers and kallikrein inhibitors. For C1-INH replacement therapies, to which Cirynze belongs, there are two plasma-derived products (Cinryze, Berinert) and one recombinant human product (Ruconest) (Caballero, 2021; Longhurst and Bork, 2019). HAE is therefore a disease characterised by iterative innovation. Availability of treatment options for ODT, STP and LTP provides choice to prescribers to manage HAE patients. Adverse event profiles of products are different, as is the patient response. Supplier diversity has provided first- and second-line treatment options for managing adverse events, patient response and treatment adherence (Caballero, 2021; Fijen, Bork and Cohn, 2021; Longhurst and Bork, 2019). During the shortage of Cinryze, use of alternative treatment options was advised to prescribers in the EU (Shire - Direct Healthcare Professional Communication, 2017). We have not found any wider impact for patients documented in the literature, as alternative treatment options were available (EMA, 2020; Caballero, 2021). However, the manufacturer of Cinryze reported loss of revenue and competitive position, as patients were moved to alternative treatments, evidencing a well-functioning market (Palmer, 2017). Although not commonly seen in markets for rare diseases, the increasing number of approved therapies for HAE may result in competition between medicine manufacturers, potentially decreasing the cost of therapies and increasing treatment affordability (Lumry, 2018)

In rare diseases where the risk of a shortage is a real threat, **diversity of supply saves patients from experiencing huge health losses from shortages**. Furthermore, **a diversified supply** composed by iteratively improved classes of products and treatments **helps deliver optimal treatment to patients suffering rare diseases while promoting competition and an efficiently functioning market**.

4. Review of policy: countries position around supplier diversity

4.1. Current policy landscape

The following section discusses the current state of policies focusing on RDs, along with those that either implicitly or explicitly serve to promote or impede supplier diversity in medicine markets. This discussion will focus on the EU, Australia, Belgium, Canada, Denmark, France, Germany, the Netherlands, and the United Kingdom.

4.1.1. Policies promoting medicines for RDs

The EU has established several initiatives with the aim of supporting those living with RDs, as promoting research and innovation in the RD space has been a long-standing goal for the EU. The adoption of the Orphan Regulation, which established orphan designations for RD medicines, in 2000 demonstrated the EU's commitment to fostering a research environment that promotes the development of medicines for RDs (European Commission, 2024b). Moreover, since 2007, over €3 billion has been invested into RD-related projects via the Seventh Framework Programme, Horizon 2020, and Horizon Europe (European Commission, 2024b).

Additionally, in 2009, the European Commission issued a recommendation requesting that all EU member states create and implement a national framework or strategy on RDs (European Commission, 2024b). In accordance with this recommendation, the EU established the European Project for RDs National Plan Development (EUROPLAN) to support member states in creating these plans (Adachi et al., 2023).

As such, all the former and current EU member states have RD strategies in place, as do Canada and Australia (the non-European countries under study). Table 3 enumerates the key measures taken or recommendations of these various national strategies, demonstrating that – while these frameworks might vary in specifics – they all tend to focus on similar themes, such as promoting the coordination of care, improving diagnosis, increasing access to and availability of medicines, and promoting research into, and medicines for, RDs (Australian Government Department of Health and Aged Care, 2020; Canada, 2021; Department of Health, 2013; EUCERD, 2013, 2014, 2015; Health Canada, 2023; NAMSE, 2013; Onkelinx, 2013; Pennington, Jorgensen and Wall, 2023; Sundhedsstyrelsen, 2014; ZonMw, 2013).

TABLE 3 KEY POINTS OF NATIONAL RD STRATEGIES

Specific measures taken or recommended in RD National Strategy/Plans[1]	Examples of countries that explicitly include this measure in their RD plan	Description / examples
Empower patients with RDs		e.g., improve patient involvement in the provision of care and promote RD patient groups as key partners

[1] *(Australian Government Department of Health and Aged Care, 2020; Canada, 2021; Department of Health, 2013; EUCERD, 2013, 2014, 2015; Health Canada, 2023; NAMSE, 2013; Onkelinx, 2013; Pennington, Jorgensen and Wall, 2023; Sundhedsstyrelsen, 2014; ZonMw, 2013)*

Improve information availability and knowledge		e.g., ensure physicians are knowledgeable about various RDs and increase everyone's knowledge and awareness of RDs
Ensure quicker diagnostics		e.g., promote screening measures and genetic testing
Coordinating care		e.g., having a named care coordinator for individuals with RDs and using telemedicine and IT
Establish/improve centres specifically for RDs		e.g., formalise a network of specialist centres that is easily accessible and connect specialist centres with others in Europe
Promote research into RDs and treatments		e.g., develop a national research strategy and address gaps in areas that are important to RD patients
Improve access to treatments		e.g., ensure treatments are available regardless of location and that patients get timely access to medicines

Key							
Australia 	Belgium 	Canada 	Denmark 	France 	Germany 	Netherlands 	UK 

An objective recommended in all the countries' national plans is to improve access to and availability of medicines for RDs. Table 4 Actions Recommended to Improve Access to medicines for RDs

4 shows the various strategies these countries suggest in their plans as tools to achieve this goal.

TABLE 4 ACTIONS RECOMMENDED TO IMPROVE ACCESS TO MEDICINES FOR RDS

Specific measures taken or recommended in RD National Strategy/Plans [2]	Examples of countries that explicitly include this measure in their RD plan	Description/Examples
Improve access to treatments		All the countries have improving access to treatments as key goals in their RD plans
Generate data on off-label use		Collect data on how patients are responding to off-label use of treatments to identify further treatment options
Compassionate use of orphan medicines		Allow patients to use medicines that have not been authorised yet
Promote accelerated access to treatments for RDs		e.g., allow for the fast-tracking of medicines through the assessment process
Consideration of RD-specific characteristics and expertise at HTA/reimbursement		e.g., broaden HTA processes to address challenges for technologies for RDs, ensure that

[2] *(Australian Government Department of Health and Aged Care, 2020; Canada, 2021; Department of Health, 2013; EUCERD, 2013, 2014, 2015; Health Canada, 2023; NAMSE, 2013; Onkelinx, 2013; Pennington, Jorgensen and Wall, 2023; Sundhedsstyrelsen, 2014; ZonMw, 2013)*

					HTA and reimbursement bodies have RD expertise		
Key							
Australia	Belgium	Canada	Denmark	France	Germany	Netherlands	UK

Most countries in this review have aspects of their HTA and reimbursement processes that promote market penetration by orphan medicines, which are detailed in Table 55.

TABLE 5 CONSIDERATIONS IN HTA AND/OR REIMBURSEMENT PROCESSES

Measure taken in HTA/reimbursement processes[3]	Examples of countries that have this measure for RD medicines	Description/Example
Special considerations for orphan medicines in HTA and/or reimbursement		These countries have considerations in their HTA and reimbursement processes — either in writing or in practice — for orphan medicines
Additional benefit of orphan medicine is considered proven at marketing authorization when budget impact threshold applies		Therapeutic value is taken as given if the budget impact is not above €30 million in Germany
Accelerated HTA procedure is available for orphan medicine		France offers an accelerated pathway for innovative medicines (including non-orphans), and Belgium lets some orphan medicine companies start the price-setting process earlier. Other countries can have some form of accelerated or early access schemes for innovative medicines that may have not been captured here because they are specific for medicines for rare diseases, regardless of whether they are orphan medicines.
Separate HTA process for orphan medicines		Medicines for RDs that receive a negative reimbursement decision in Australia can re-apply under the LSDP. The UK has the HST process specific to orphan medicines meeting a stringent set of criteria.
Flexibility in level of evidence for orphan medicines		Orphan medicines filing a Class I application in Belgium do not need to submit a pharmaco-economic model. In Germany,

[3] *(Gammie, Lu and Babar, 2015; German Market Access – Simplified, 2024; Facey and Nicod, 2019; Stafinski et al., 2022; Koyuncu, 2022; Abdallah et al., 2022)*

		France, and Canada, rarity is a key consideration in guiding HTA and reimbursement decisions when there is uncertainty about available evidence.
Cost-effectiveness or budget impact used as assessment criteria		HTA decisions are contingent upon cost-effectiveness or budget impact of the technologies at hand
Therapeutic advantage used as assessment criteria		e.g., France and Germany assign ratings to medicines based on their added therapeutic value, and make HTA decisions accordingly

Key							
Australia	Belgium	Canada	Denmark	France	Germany	Netherlands	UK

The United Kingdom and Australia have separate processes for orphan medicines, with the United Kingdom applying its Highly Specialized Technology (HST) evaluation for specific orphan medicines that meet stringent criteria, from the outset of the HTA process (NICE, 2022), and with Australia allowing for specific medicines that receive negative reimbursement decisions in the standard process to be reassessed under its Life Saving Drug Program (LSDP) (Stafinski et al., 2022). In Germany, orphan medicines' therapeutic values are taken as given upon regulatory approval, as long as their budget impacts are not greater than €30 million (Stafinski et al., 2022; Koyuncu, 2022). In Belgium, orphan medicines follow the same process as non-orphan medicines; however, pharmaceutical companies are generally not required to submit a pharmacoeconomic evaluation, and companies can start the price-setting procedures earlier (Abdallah et al., 2022; Facey and Nicod, 2019). Canada has no special considerations in place for orphan medicines in the HTA process – other than rarity being considered when evidence is uncertain – but some of its provinces have considerations in place for medicines for RD in their own processes (Facey and Nicod, 2019; Pant and Visintini, 2018). Denmark, in contrast to the aforementioned countries, has no special considerations in place for orphan medicines in its HTA processes (Facey and Nicod, 2019).

The EU encourages R&D in orphan medicines through the EU Regulation on orphan medicinal products (OMP) (European Commission, 2024a; Berdud et al., 2020).The EU Regulation on OMP incentivises approved medicines that receive orphan designations by providing a fixed market exclusivity period of ten years, as well as fee reductions for pharmaceutical companies at the application for marketing authorisation to the EMA. Australia similarly has an orphan drug act, though it does not provide market exclusivity for orphan medicines; rather, it primarily incentivises the development of orphan medicines through fee waivers (Therapeutic Goods Administration, 2015). Canada, in contrast to the EU and Australia, does not have its own national orphan drug legislation (Franco, 2013; Rawson and Adams, 2024).

These policies, taken as a whole, are indicative of EU-level and country-level concerns about increasing access to treatment in the RD space and improving the lives of those living with RDs.

4.1.2. Policies promoting and discouraging diversity of supply

People with RDs, health care systems, and RD markets in general are especially vulnerable to risks associated with single suppliers, and they are potentially big beneficiaries of supplier diversity.

Countries and policy makers are not insensitive to this. In some aspects of decision-making, policies and recommendations at the EU and country level have promoted supplier diversity for various reasons. Yet, at the same time, certain strategies within the pharmaceutical market have the opposite effect of promoting single-supplier markets.

Indeed, procurement, reimbursement, and HTA procedures play a significant role in shaping market conditions. For one, most countries use tendering as a procurement strategy for pharmaceuticals in hospital care, and some countries have adopted tendering for outpatient care as well (Kanavos, Seeley and Vandoros, 2009). Tendering has historically been used in off-patent markets, but it is increasingly being used in the on-patent market due to its ability to induce price competition (Barrenho et al., 2023). Tenders and tender-like procurement strategies, such as the Netherlands' preference policy, have the potential to promote monopoly-like conditions when they award single manufacturers (Barrenho et al., 2023; Surhake, 2024).

Countries have begun moving away from winner-takes-all tenders because of the link between single-supplier markets and potential medicine shortages. France, for instance, historically used winner-takes-all tenders for pharmaceuticals, which led to product withdrawals and shortages in some cases. In response, France now partly uses two-winner tenders in an attempt to maintain competition and prevent medicine shortages (EFPIA, 2022).

In acknowledgement of the risk of single-winner tenders, the European Federation of Pharmaceutical Industries and Associations (EFPIA) published a white paper on effective public procurement of medicines in the EU, advising that countries in Europe avoid "'price-only and winner-takes-all awards" and allow for multiple winners with the aim of preventing shortages (EFPIA, 2022). Similarly, the EU's Pharmaceutical Strategy for Europe advises member states to avoid using single-winner, price-only tenders due to their link to medicine shortages and insecure supply (European Parliament, 2021).

HTA and reimbursement procedures can also play a role in promoting single-supplier markets and, consequently, discouraging competition and diversity of supply. Germany and France, for instance, provide ratings for clinical added value, and medicines with ratings indicating no added value relative to comparators on the market are more likely to receive negative pricing decisions (Nijhuis, Guan and Tewary, 2019). The European Parliament's resolution to improve access to medicines points to the role that HTA processes and criteria can play in limiting medicine accessibility and availability, and affirms the European Parliament's support for a multi-disciplinary approach to HTA that considers various criteria such as real therapeutic added value, social impact, budget impact, sustainability of the health system, and the cost-benefit of the technology (European Parliament, 2017). Additionally, the European Parliament specifically acknowledges that follow-on — or 'me-too' — medicines can have value in terms of incremental innovation and patient care (European Parliament, 2017).

Outside of HTA and procurement strategies, efforts to address medicine shortages have called for supplier diversity due to the aforementioned links between single-supplier markets and supply insecurity. Table 3 outlines some of the measures being taken or recommended by these countries and the EU. Every one of the countries in this discussion has taken measures to prevent or manage medicine shortages, such as requiring shortage reporting by marketing authorisation holders (MAHs), imposing mandatory stock requirements, or requiring MAHs to create shortage management/prevention plans. Canada, Germany, the United Kingdom, and the EU have all established guidance or recommendations or passed policies promoting supply chain diversification as a strategy to prevent medicine shortages.

TABLE 3 MEASURES TAKEN/RECOMMENDED TO PREVENT OR MANAGE MEDICINE SHORTAGES

Measure taken/recommended to prevent or manage shortages?	Examples of countries explicitly including these measures	Descriptions/Examples
Mandatory Reporting[4]		Marketing authorisation holders (MAHs) are required to notify relevant national agencies that there might be a risk of a shortage
Shortage Database[5]		Shortage information is available on databases
Mandatory Stock Requirements[6]		Requirement of stockpile of critical medicines for a certain number of months
Pricing Adjustments[7]		The UK offers price concessions to pharmacists, and Germany can increase reference prices by 50%
Shortage Management/Prevention Plan[8]		MAHs are required or encouraged to have shortage management/prevention plans in place either prior to or in response to shortages
Export Restrictions[9]		The UK has a list of medicines that cannot be exported, and Canada and Belgium prevent medicines from being distributed outside of the country if it could worsen shortage risks
Promoting Domestic Production/Reshoring[10]		Reduce manufacturing reliance on single/few countries and promote domestic manufacturing
Supply Diversification[11]		e.g., general recommendations to diversify supply chains, reduce sole supplier contracts, and promote multiple-supplier frameworks

Key

Australia	Belgium	Canada	Denmark	France	Germany	Netherlands	UK	EU
								

[4] *(ABPI, 2024; Bocquet et al., 2017; Department of Health and Aged Care, 2024; Di Trapani, 2019; Ravela, Airaksinen and Lyles, 2023; Danish Medicines Agency, 2023; Koyuncu, 2023; EMA, 2023)*
[5] *(ABPI, 2024; Acosta et al., 2019; BfArM, 2024; Department of Health and Aged Care, 2024; European Commission, 2023; KNMP Farmanco, 2024; Drug Shortages Canada, 2024)*
[6] *(Euronews, 2024; Australian Government Department of Health and Aged Care, 2024; Public Health Agency of Canada, 2004; RFI, 2024; Medicines for Europe, 2024; Buch Henrichsen and Kaas-Petersen, 2024; Schwaiger, 2024; Koyuncu, 2023)*
[7] *(Duddy, 2024; Koyuncu, 2023)*
[8] *(Belgodère et al., 2023; Health Canada, 2024b; EMA, 2023; Department of Health & Social Care, 2024)*
[9] *(Health Canada, 2024a; Chini, 2019; ABPI, 2024)*
[10] *(Global Trade Alert, 2022; Federal Government of Germany, 2023; European Commission, 2023; Martuscelli, 2023; Le Monde and AFP, 2023; Economic and Social Council, 2021)*
[11] *(MSSC, 2017; Federal Government of Germany, 2023; Department for Business & Trade, 2024; European Parliament, 2021)*

In 2012, Canada's House of Commons Standing Committee criticized sole-source contracting as the most avoidable cause of medicines shortages in a report on medicine supply (Smith, 2012). As a result, a multi-stakeholder steering committee on medicine shortages (MSSC) issued guidance recommending supply chain diversification and contracting with multiple suppliers (MSSC, 2017). Similarly, Germany published a pharmaceutical strategy "Improving the policy environment for the pharmaceutical sector in Germany," wherein a key aspect of the strategy is to diversify supply chains (Federal Government of Germany, 2023). However, this "diversification" is mostly focused on preventing reliance on singular countries (i.e. China for manufacturing). The United Kingdom recently published its "UK critical imports and supply chain strategy," which specifically calls on the NHS to "implement multiple supplier framework agreements to improve the security of supply and to manage demand spikes or individual supplier challenges" (Department for Business & Trade, 2024). Likewise, the European Pharmaceutical Strategy highlights the importance of enhancing medicine supply chains to avoid shortages; it specifically suggests that a key recommendation for preventing shortages could involve diversifying supply chains and production (European Commission, 2024). Additionally, the EU established the Critical Medicines Alliance (CMA) in 2024 with the goal of reducing shortages in critical medicines, and one of its recommendations is to encourage diversification within the supply chain for critical medicines (European Commission, 2024a). These recommendations underscore policymakers' recognition that bottlenecks in supply chains could increase the risk of shortages. This occurs either due to disruptions from a major global supplier of key inputs or a sudden surge in demand that a concentrated supply chain cannot quickly adapt to meet. Such a policy strategy aligns with promoting multiple suppliers or treatment options, as doing so would likely create separate and diversified supply chains, allowing for the use of a medicine in the case of a supply chain bottleneck for another medicine.

4.2. Policy assessment analysis

National RD plans of Australia, France, and the Netherlands identify HTA and reimbursement processes as areas in which characteristics of RDs ought to be considered to improve access to medicines for those with RDs (see Table 4 Actions Recommended to Improve Access to medicines for RDs

). Germany and the United Kingdom make brief mentions of potentially reassessing reimbursement and cost-benefit assessments of orphan medicines. While these are the only national strategies that explicitly mention this approach to increasing RD medicine availability, all countries under study but Denmark have specific aspects promoting access to orphan medicine into their HTA and reimbursement processes. Notably, these considerations only apply to medicines with the orphan designations, with the exception of France's expedited HTA process, which applies to innovative medicines (Armoiry et al., 2019). While this approach based on orphan designations has been proven effective in incentivising the development of new medicines for RDs (Miller, Fermaglich and Maynard, 2021; Neez et al., 2020; Berdud et al., 2020), the ability to access alternative available therapies for RD indications should not be impaired. National RD plans, and HTA and reimbursement incentives should be adapted to combine orphan medicine incentives with maximum access to available RD treatment options, guided by a cost-benefit assessment that fully considers the benefits afforded by having additional available treatments (i.e. those mentioned in section 3.2) alongside the relevant costs. Such a policy strategy will have multiple advantages associated with supplier diversity as this report has shown in section 3.

It is worth highlighting that we have only found two EU countries, France and Belgium, that include 'accelerated access to treatments for RD' as a specific action for 'improving access to available

therapies' within their RD strategies specifically (see Table 4 Actions Recommended to Improve Access to medicines for RDs

). This is consistently replicated by the HTA and reimbursement processes for these two countries, as Belgium allows some orphan medicines to start the price-setting process earlier, and France fast-tracks medicines deemed 'innovative,' which can include certain orphan products (Facey and Nicod, 2019; Stafinski et al., 2022). While fast-track pathways may accelerate the time to market for first-in-class products, they are unlikely to address the pace at which second or third entrants are adopted—or whether these entrants have sufficient incentives to enter the market at all. In any case, both recommendations for accelerated access are not confirmed by countries' performances in providing fast access to treatments for RDs. While France is ranked within the top-3 countries in terms of orphan medicine availability in the W.A.I.T indicator, which details orphan medicine availability and time to market in various EU member states, its rank decreases significantly in considering the median time to availability (EFPIA - W.A.I.T., 2024). Belgium's rank for availability is around the EU average and also decreases for time to availability (EFPIA - W.A.I.T., 2024).

Only Australia, France, and the Netherlands have specific action recommendations in their RD plans for considering particular characteristics of RDs and RD expertise in their HTA and reimbursement processes. In our review, neither Canada nor the United Kingdom complement the high-level claim for improved access plans for RDs with any specific action that can be considered under any of the themes identified. However, the United Kingdom has the targeted HTA process for orphan medicines meeting specific criteria, which is a specialised RD plan in action at HTA-level. This is not happening in Canada at a central level, as Canada's RD strategy represents a slightly different approach, and entails a funding commitment to support, diagnosis, research, and treatments for RDs. Denmark only contemplates compassionate use as a potential element to improve access to RD medicines in its RD plan, which is complemented with cost-effectiveness or budget impact criteria for assessment at HTA. The design of HTA processes and reimbursement decision frameworks is important for optimising access to therapies for RDs. In particular, a narrow view of added therapeutic value (e.g. only focusing on clinical outcomes) can prevent market access by available follow-on medicines that have a similar therapeutic value as comparators. Indeed, a report by IQVIA — commissioned by EFPIA — on person-centred therapeutic innovations, identified that there exists a conflict between payers, physicians, and patients in perceptions of follow-on medicines (Nijhuis, Guan and Tewary, 2019). While payers tend to believe that follow-on medicines offer only marginal improvements, physicians value the flexibility in treatment options afforded by follow-on medicines, and patients value follow-on medicines' improvements in usage experience (Nijhuis, Guan and Tewary, 2019).

For example, the HTA framework in France is not favourable for promoting multiple suppliers in markets for RDs when multiple new medicines are available and no significant therapeutic differences between them exist (e.g., follow-on therapies). HTA and reimbursement in Germany are also driven by added therapeutic value, and this has similar effects. While added therapeutic value is an effective value-based incentive to pull innovations of higher benefit for patients, its practical implementation should be designed to avoid any negative interaction with the access to, and the availability of, existing effective alternative therapies. Especially in RDs, where a high proportion of markets are characterised by single suppliers and small populations, a strong preference only for products showing significant added value in these markets may contribute to exacerbate the risk associated with single suppliers (e.g., risks and impacts of shortages). This is recognised by the European Parliament's resolution on improving access to medicines, which provides support for a multi-criteria-driven HTA and includes an additional mention recognizing follow-on medicines' role in inducing iterative innovation (European Parliament, 2017).

This is particularly relevant considering that much of the work done to achieve countries' policy aims of improving access to and availability of treatments for people with RDs is focused specifically on orphan medicines; less can be said about access to RD medicines without orphan designations — and follow-on RD medicines are likely to fall into this category. That is, even though every country in this review has the expressed goal of enhancing access to RD treatments, improving access to non-orphan RD medicines has not been a policy priority. HTA and reimbursement processes that fail to consider rarity for non-orphan RD medicines are likely to have the effect of limiting the number of available RD treatments, as it is more difficult for RD medicines to meet standard evidentiary requirements due to small patient populations. France recognises the importance of having multiple winners and suppliers in markets to avoid risks of single suppliers. Tendering processes are moving to two-winner options to mitigate risks of monopoly-served markets (EFPIA, 2022). This concern is also shared by EFPIA and the EU, which both advise avoiding winner-takes-all tendering approaches driven by most favourable price criterion to tackle risks of single-supplier markets (EFPIA, 2022).

Beyond procurement process design and tenders, considerations for supplier diversity are also included in the shortage prevention policies and plans reviewed. Supply diversification is a key measure for shortage prevention and management included in guidance and policies issued by the EU, the United Kingdom, Germany, and Canada. The EU includes diversification of supply chains as a powerful measure to avoid shortages and their risks in the new pharmaceutical legislation proposal (European Commission, 2024), but this is not currently visible in member states other than Germany. Moreover, it is misaligned with some of the HTA/reimbursement processes and considerations for RDs previously highlighted in this section e.g., France, Germany, Belgium.

Though Germany makes mention of supply chain diversification in its strategy to improve the policy environment for pharmaceuticals, it ties this diversification to proposals to promote EU-based manufacturing, so as to avoid reliance on a few or single countries (e.g., China and India) (Federal Government of Germany, 2023). The other EU countries in this discussion – with the exception of Denmark -- have similarly promoted reshoring pharmaceutical manufacturing in this way, which is aligned with EU policy recommendations (European Commission, 2023; Economic and Social Council, 2021; Martuscelli, 2023; Le Monde and AFP, 2023). Measures proposed to achieve this goal include examining incentive systems for manufacturing sites, amending EU procurement laws with a view toward domestic manufacturing, and potentially providing subsidies for the production of critical medicines and off-brand pharmaceuticals (Federal Government of Germany, 2023; Martuscelli, 2023). Thus, while these countries are not necessarily mentioning supply chain diversification as key tenets by which they can prevent shortages, they are implicitly recognizing that reliance on a single or few manufacturing countries increases the risk of shortages. However, achieving this goal will likely see buyers facing increased prices for medicines — even with potential subsidies — due to higher labour costs and stricter environmental regulations than Asian countries, which are currently large producers of medicines (Martuscelli, 2023). Promoting access to more treatment options is a policy recommendation that could align with these nations' efforts to diversify supply chain and reduce reliance on single countries; having two treatment options provides potentially alternative supply chains, meaning that if a bottleneck occurs for one medicine, resulting in a shortage, the other option could still be available for patient use.

5. Discussion

In this report, through a literature review, we have explored and discussed the risks of single suppliers, and the value added by supplier diversity in medicine markets for RDs. To evidence the findings of the literature review, we have developed a series of seven case studies that illustrate with real examples the findings in the literature. We have also reviewed the EU-level and some countries' relevant policies regarding the supplier diversity for medicine markets for RDs. We have performed a targeted literature search to identify the most relevant policy documents for our policy analysis. Identified documents have been reviewed and critically assessed thereafter.

Supported by the literature review, we have evidenced the risks of single-supplier medicine markets. The main risk of single suppliers that we have identified is the risk of shortages and supply disruptions. This is mainly due to the inability to switch patients to an equivalent treatment alternative. Evidence suggests shortages in markets with single suppliers disproportionately affect patients, leading them to suffer potentially huge health losses.

This risk is amplified in markets for RD medicines, due to: the small market size characterising RDs and the lack of incentives to manufacture and compete in these markets; the lack of physician and patient choice and treatment alternatives; the fact that RDs are chronically debilitating and can be life threatening, which means they may suffer more serious consequences in case of a treatment discontinuation; and because treatments for RDs tend to be biologics, which are difficult to manufacture and handle, making shortages of these medicines especially challenging to navigate.

The Fabrazyme case study illustrates how the lack of effective treatment alternatives was a risk for patients' health in markets for RDs. In the US, where there was only one approved treatment for Fabry disease, approximately 80% of patients went without treatment for several months, leading to clinical deterioration including pain, fatigue and one reported death. The reason for the shortage in the case study was contamination, which is illustrative of the relatively higher risk of a shortage for biologics, which have more complex manufacturing processes.

Procurement and pricing and reimbursement policies can also contribute to higher risk of shortages in the long-term, with short-term effects in the shape of repeated acute supply disruptions. The literature review shows that tendering of single-supplier winners is considered a risk factor for medicine shortages. A winner-takes-all approach in tenders erodes supply resilience making markets highly dependent on a sole manufacturer. In cases where the sole supplier suffers a shortage, existing alternatives that did not win the tender would not be ready to plan and execute production immediately. The studies we reviewed identified the link that exists between the use of tenders and sole supplier or concentrated markets, which is associated with higher risk of shortages. However, the causality of this tender-shortage relationship remains an unaddressed research question in this area of the literature and would benefit from further research.

More generally high market concentration is also correlated with higher risk of shortages as our review of the literature shows. A reduced number of competitors in a market are less capable to meet higher patient demand when a shortage occurs. The literature establishes a negative correlation between the number of competitors and the risk of a shortage in the US, Europe, and Canada.

The Cerezyme case study also exemplifies the risk of health loss for patients when effective treatment alternatives are missing. In Gaucher disease patients who discontinue treatment, or were treated with lower doses, suffered evident clinical deterioration including symptoms like fatigue, bone

infarction, bone pain, or hepatomegaly. Regulators identified alternative treatment manufacturers in late-stage clinical development to mitigate the impact, while a new treatment was also licensed during the shortage. This demonstrates that a diversified supply can ameliorate the impact of a shortage.

We have also documented the value added by supplier diversity with the findings of our literature review. Supplier diversity is associated with iterative innovation, the staged and cumulative process that characterises pharmaceutical innovation. In mature markets, the outcome of that process is the availability of multiple therapies of different classes, oftentimes with more than one (or even several) follow-on alternatives competing within each class. This results in expanded access, affordable innovations, health system sustainability, and most importantly, enhanced patient and physician choice.

We have evidenced the benefits of iterative innovation, and the value added by supplier diversity with the Haemophilia case study. The main lesson from the study of the haemophilia innovation is that continued investment in R&D and innovation led to the development and approval of numerous innovations. More specifically, the emergence of multiple plasma and non-plasma derived clotting replacement factors in the same class promoted competition and expanded access to life-changing therapies for haemophilia patients.

Our analysis of the literature also shows that promoting access to multiple available treatments in RDs is a strategy that provides insurance value to patients in the event of a shortage. The full insurance value for RDs is still to be unlocked as markets for RDs are typically characterised by a single or small number of suppliers of alternative treatments. This potential benefit still to be realised is documented with the DMD case study. DMD is a disease with multiple suppliers developing and providing experimental treatments which has created an environment that fosters competition, enhances patient health, and drives scientific advancements, not only for DMD but also for RDs. However, although it is a good emerging illustration of iterative innovation, its value still remains unlocked in the EU where the only available targeted therapy (Ataluren) has recently been withdrawn, leaving patients with no treatment options available while the first gene therapy for DMD is still under review.

Supplier diversity is also linked to in-class competition, which is associated with multiple benefits including price competition, expenditure control and promotion of health system sustainability. New products need to seek their market niche by addressing remaining unmet need when a class gets saturated with competitors, hence it also drives innovation and medicine R&D towards addressing remaining unmet need. We can conclude that in-class competition is a natural step of iterative innovation and diversified supply value generation factor.

The design of tenders to allow availability of 'follow-on' medicines and competition can be an efficient procurement mechanism offering all benefits of supplier diversity. Multiple-winner tenders, when well designed, can offer the cost-saving benefits of single-winner tenders while they promote better supply-chain resilience. In the case of RDs, we propose that promotion of supplier diversity with multiple-winner tenders is important as - given the small market size - it is a challenge for competitors that did not win to stay on the market. Manufacturing capacity and supply can take months to adapt to a changing demand, and it is costly to keep it in standby until the next tender. Therefore, having multiple suppliers is a safer strategy for patients and health care system resilience.

The Cinryze case study illustrates the amplified supply challenges for RDs and biologics and the benefits of the supplier diversity. In 2017, a problem with a CMO resulted in an international product shortage. Even though the marketing authorisation holder had enough manufacturing capacity by the time of the shortage to meet the demand, it took months until batches produced in some recently acquired plants were released by the quality control. However, alternatives were available resulting in

no (documented) patient losses and market competition. Diversity of supply protected patients' health during the shortage and promoted competition in well-functioning markets.

The policy review documented various initiatives promoting the availability of medicines for RDs, such as national plans identifying this as a key goal and HTA considerations specifically in place for orphan medicines. Additionally, it discussed various policies that have the effect of reducing supplier diversity, such as tendering and strict HTA criteria that focus only on added therapeutic value, as well as policies that encourage supplier diversity — especially those related to preventing medicine shortages. The review also highlighted some of the contradictions that exist between these policies.

Indeed, all the countries in the policy review have an expressed interest in promoting the accessibility and availability of RD medicines, as each country has a national strategy with an explicit mention of this goal. In alignment with this objective, many of the countries have special considerations in place in their HTA and reimbursement processes for orphan medicines. However, as previously mentioned, these considerations only apply to medicines with orphan designations; consequently, follow-on medicines for RDs, which do not have orphan designations, are often not the beneficiaries of these considerations. This means that they must go through the same HTA and reimbursement processes as non-RD medicines. This could place these medicines at a disadvantage in receiving a positive HTA or reimbursement decision, particularly given that medicines for RDs have smaller patient populations, making standard evidentiary requirements more difficult to satisfy. In effect, this does not align with countries' stated goals of improving the availability and accessibility of RD medicines.

Alternative therapies for RDs may face additional obstacles in countries that place a significant emphasis on added therapeutic value in their HTA criteria — such as France and Germany — as this focus can lead to equally effective medicines receiving negative reimbursement decisions. This could have the effect of limiting patient and physician choice in the RD space, and it also could prevent further data generation on how patients with RDs respond to treatment alternatives.

The policy review also discussed how a reliance on tendering as a procurement mechanism can give rise to single-supplier markets. Single-winner tendering, in particular, has been criticized at the EU- and country-level for its link to medicine shortages. This criticism has not, however, been extended to other policies that promote single-supplier markets, such as HTA policies that limit market penetration by follow-on medicines or alternative therapies with similar levels of clinical effectiveness.

Policies focusing on diversifying supply chains have been aimed at reducing reliance on single or few manufacturers and preventing bottlenecks within the supply chain. As mentioned within the review, including treatment alternatives is a policy that is in alignment with these strategies, as it would reduce reliance on a singular supply chain altogether, allowing for a treatment option to be available for use in the case of a shortage of another.

It should be noted that while all the countries in the policy review have policies relating to preventing medicine shortages and objectives of improving the availability and accessibility of RD medicines, there exists very little guidance at any level about preventing shortages in the RD space. Given the fact that most RD patients who have a medicine on the market for their disease only have one option available, this is a particularly relevant issue, as a shortage of their available treatment could lead to significant harm. As such, this is a gap that is yet to be addressed in much of the policy work surrounding RDs.

6. Conclusions and recommendations

Several policies and incentives have been introduced at regulatory and reimbursement levels to stimulate R&D in RDs and provide treatment options for RD patients. While these measures have stimulated the development of new treatments, there often remains a lack of competition and treatment alternatives even after market exclusivity periods expire. Our aim was to document and discuss the risks associated with single suppliers and the benefits of supplier diversity in RD medicine markets.

We show that reliance on sole suppliers can have negative implications for both patients and healthcare systems at large, as single-supplier markets can be more prone to medicine shortages, which can harm patients' health when alternative treatment options do not exist. We conclude this risk is even more amplified in the RD space, as RDs are likely to be chronic and seriously debilitating, and in the market for biologics, which involve complex manufacturing processes that cannot easily adjust to market shocks.

We also highlight the benefits that supplier diversity can generate for healthcare markets. Well-functioning medicine markets enable investments to drive iterative innovation that can address remaining unmet need, provide patients with multiple therapies of different classes, expand in-class competition, and generate knowledge spillovers. Additionally, supplier diversity can mitigate the risk of shortages to patients, who can be switched to other existing therapies. Finally, increased competition amongst diverse suppliers may contribute to more affordable innovation and health system sustainability.

Procurement policies are not always aligned with the benefits of having supplier diversity in markets for RD medicines. Use of single-winner tenders (e.g. winner-takes-all) and other preferred supplier contracting approaches that rely on single suppliers are associated with all the aforementioned risks. Overall, we identified that, beyond market shock risks like peak demand, there are policy-induced risks, such as those from procurement or tendering processes. Importantly, these policy-induced risks can be mitigated through targeted policy action. Ideally, policy at all levels should reflect the value added of supplier diversity. Our policy analysis shows that this is not always the case, presenting an opportunity to recognise the value of supplier diversity more widely.

High-level policy and national strategies can promote sustainable and resilient medicine supplies. While there is recognition of medicine shortages as a critical issue in non-RD-specific policies and strategies, there is room to expand RD policies to prioritize medicine shortage mitigation and supply resilience by promoting and improving supplier diversity.

HTA, pricing and reimbursement, and procurement policies can help reduce barriers to availability of medicines and supplier diversity. While it is necessary to ensure that value-based assessments remain a core element of HTA and decision-making in order to reward all types of innovation (radical and more incremental innovation), the value added by available treatment alternatives and supplier diversity should be recognised and used to complement pricing and reimbursement decisions.

Finally, procurement mechanisms can play a pivotal role in the promotion of supplier diversity and competition by adopting more targeted and inclusive decision rules for public procurement or prioritising multiple-winner tender designs over winner-takes-all tenders. This would contribute to expanded access to innovation and improved healthcare system resilience against the risk of shortages.

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