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Re-Thinking Rare Disease

by Melanie Senior

Germany is drastically squeezing orphan drug pricing while new US laws protect rare diseases drugs from price negotiations. These contrasting moves fuel the longstanding debate over whether orphans still deserve special incentives.

In the last days of July 2022, Germany's cabinet passed a swathe of drug pricing measures designed to curb pharmaceutical spending and help plug a €17bn healthcare funding gap in 2023. (Also see "*Germany: Leaked Pricing Measures Could Have 'Drastic' Consequences For Orphans*" - Pink Sheet, 7 Jul, 2022.) Weeks later, US Congress passed a law allowing Medicare to negotiate the prices of some drugs, potentially saving $100 billion over a decade. (Also see "*Medicare Price 'Negotiation' Process Gets Broad Brush Treatment In New Law*" - Scrip, 16 Aug, 2022.) But while Germany's new laws include a drastic squeeze on how orphan drugs are assessed and priced, the US law protects the category – and may even provoke higher launch prices.

Payers everywhere are concerned over the growing collective cost of rare diseases drugs. They account for over half of FDA approvals and 40% of the global pipeline, yet ultimately serve less than 10% of the population. Their median drug price approaches $170,000 and some one-time treatments cost over 20 times *that*. In 2026, each of the ten highest-selling orphans will be worth between $3bn and $13bn, according to Evaluate.

Hence long-standing questions over whether the 1983 US Orphan Drug Act and its European equivalent are still fit for purpose. These laws have worked extraordinarily well to incentivize R&D into rare conditions, using a suite of tax credits, extended market exclusivity periods and waived regulatory fees. Many orphan drugs also benefit from expedited approval pathways with lower evidence hurdles.

This landscape has resulted in important, often life-saving treatments for hundreds and thousands of patients. It has spawned dozens of rare-diseases-focused biopharma companies, including in now-crowded corners like gene and cell therapy that lend themselves to the rare-diseases approach. Big Pharma has been drawn in, too: orphans will make up almost 40% of *Johnson & Johnson*'s pharma sales by 2026.

There are no moves to tamper with the US Orphan Drug Act. A consultation on *proposed changes* to Europe's orphan regulations – including shorter exclusivity periods – has not yet led to action either. The apparently divergent German and US pricing approaches add urgency to this debate. Are orphan drug incentives now backfiring, by pulling R&D dollars away from more widespread conditions that cost health systems and societies more dearly? Or does the innovation engine still need this orphan-focused fuel to keep running effectively?

Ultimately, a balance is needed, which, at first glance, neither nation appears to have achieved. In the meantime, the gap between orphan drug access in the US and Europe is likely to widen.

Abolished Privileges

Germany has moved decisively to re-set thresholds within its already strict rules-based approach to pricing and reimbursement. Orphan drugs, classified as those destined for fewer than five in 10,000 people in Europe (about 230,000 people), currently escape the normal added-benefit review that other new medicines are subjected to – unless and until they sell more than €50m a year. This loophole irked the country's health technology assessment body, IQWiG. It found, in *January 2022*, that over half of orphans that did go on to be assessed failed to show any additional benefit. So, declared IQWiG director Juergen Windeler, "it's time to abolish the privilege of fictitious added benefit for orphan drugs."

His agency's call for action was one important voice influencing the resulting *GKV-Finanzstabilisierungsgesetz* – public health insurance financial stability law—which cuts the annual sales threshold to €20m. That will mean many more orphan drugs are assessed and receive a benefit rating. Few are likely to score highly, given the difficulties of generating adequate evidence from small patient numbers, and the frequent lack of appropriate comparators.

The law also tightens up the link between benefit rating and price – for instance, mandating that an "unproven" added benefit, as may be likely for orphans, must lead to a reimbursed price "reasonably lower" than the appropriate comparator therapy. (Also see "*Germany To Honor Pledge To Cut Spending On Medicines*" - Pink Sheet, 17 Mar, 2022.)

Overall, the changes will significantly impact orphan drug developers' reward. The law "is a turning point" for research-based companies in Germany, says Germany's association of

research-based pharma companies, VFA. It warns that each of the "far-reaching" pricing changes outlined in the "short-sighted, innovation-hostile" bill will interact to have a "cumulative" negative effect on innovation and investment in the country. (See Box: Show Better, Or Price Lower)

Drug companies were already pulling out of Germany. *bluebird bio* left in 2021 after failing to achieve 'value-recognition' for its newly approved gene therapy Zynteglo for beta thalassemia. (Also see "*Bluebird Exits Europe, Casting Clouds Over Gene Therapy Commercial Effort*" - Scrip, 9 Aug, 2021.) The company has since priced the therapy at $2.8m in the US. *Insmed Incorporated* in September 2022 stopped direct supplies of Arikayce, approved for a small group of patients with a rare type of lung infection, after failing to agree a price with the German association of insurance funds (GKV). Discussions are ongoing, according to the company.

Nuance Needed

Merck & Co., Inc.'s Keytruda—an orphan when first approved in the US in 2014, now with over 30 more indications and selling over $20 billion – is often cited in support of inappropriately generous orphan drug regulatory incentives. But might Germany's strong-handed approach upset the innovation-access equilibrium in the other direction?

Many of the 6000 or so rare diseases known to exist today remain under-served. Even in conditions like spinal muscular atrophy (SMA), where there are now several treatments, the heterogenous nature and trajectory of the disease means there are still patients in need. Given the challenge of gathering sufficient data from low numbers of patients, and of identifying and validating endpoints, some flexibility in evidence standards and approval pathways is reasonable.

Re-defining what counts as a 'rare' disease, strengthening post-approval

Show Better, Or Price Lower

The new public health insurance financial stability law sharpens up Germany's already-rigorous AMNOG market access framework and means that only treatments that are demonstrably superior to existing drugs will achieve higher prices. The changes include (but aren't limited to):

- Halving of free-pricing period for new drugs from 12 to six months (retrospective negotiated price applies from seventh month)
- Tighter, more precisely quantified links between added-benefit score (none, not proven, non-quantifiable, minor, considerable, major) and pricing, with more prominent role for comparator product. If the comparator is still on-patent, a new drug can only be higher priced if it achieves at least 'considerable' added benefit. If not, the reimbursed price

evidence collection, and doubling down on outcomes-based pricing agreements are among proposals put forward by the US-based Institute for Clinical and Economic Review in an April 2022 paper calling for a "next generation" of rare disease drug policy. The paper takes pains to emphasize the inevitable trade-offs from any measure seeking to re-balance affordability and innovation yet concludes that "modest" reforms are unlikely to curb resilient growth in orphan drug development.

Making 'rare' even rarer – shrinking it from the current threshold of fewer than 200,000 in the US to fewer than 50,000 or even 10,000 – makes sense in theory. Greater awareness and improved diagnostic tools are revealing conditions like transthyretin amyloidosis, which affects the heart, to be *less rare than previously thought*, calling into question the need for additional incentives.

must be "reasonably" lower than the comparator. If the appropriate comparator has not been assessed, the new drug must price 15% lower.

- Mandatory price-volume agreements and enforced price reduction on drugs with non-economic package sizing
- Current price contracts can be terminated and subject to re-negotiation
- Lower orphan drug sales threshold
- Temporary hike of mandatory rebate to 12% in 2023
- Pricing freeze for patented drugs extended to 2026

Sources: German health ministry; Aerzteblatt; National Association of Statutory Health Insurers

But agreeing a cut-off is difficult, particularly with often fluid diagnosis rates and varying geographic prevalence. Any threshold risks disincentivizing R&D for 'less-rare' rare diseases (and may lead to skewed incidence measures). In the end, the proposal to split out 'ultra-rare' conditions was one of the paper's most controversial, said ICER founder and president Steven Pearson.

Still, that is effectively what Germany's lowered annual orphan sales threshold achieves – incentives limited to drugs for the very smallest populations. England and Wales, too, have implemented a variation of this approach. The National Institute for Health & Care Excellence (NICE)'s Highly Specialised Technologies pathway applies a higher cost-effectiveness threshold to drugs treating very rare conditions impacting just one in 50,000 patients (or about 300 people), which significantly shorten life expectancy or quality and for which there is no existing therapy, or where the new option offers significant additional benefit. Yet the organisation expressly avoids committing to consider all products that meet the very-rare criteria in the HST pathway, stressing the need to "apply appropriate limits" given the resource allocation trade-off.

Pay For Outcomes

With outcomes-based reimbursement deals, orphan drug makers continue to charge the high prices that are implicitly part of the overall incentive package but agree to reimburse all or part of that cost if their treatment doesn't work as expected. Such deals are multiplying, especially for single-use gene therapies such as *Novartis AG*' SMA treatment Zolgensma or bluebird's Zynteglo, each costing millions of dollars.

bluebird in August 2022 announced it would reimburse payers up to 80% of Zynteglo's eye-watering $2.8m price tag if patients didn't maintain freedom from blood transfusions up to two years later. The rebate is more generous than those in earlier deals offered by Novartis for Zolgensma, or by *Spark Therapeutics, Inc.* for ophthalmology gene therapy Luxturna - though 20% of $2.8m, $560,000, is still a lot to pay for a drug that doesn't work as hoped. And beta thalassemia, which affects about one in 100,000, is more common than SMA or the rare retinal dystrophy addressed by Luxturna. Hence, "I'm excited about this deal, both for the magnitude of the rebate" and because "we're moving [with these deals] beyond therapies that affect perhaps only one in a million," Michael Sherman, chief medical officer at Point32Health, formed by the 2021 combination of Tufts Health Plan and Harvard Pilgrim Health Care, told *In Vivo*.

Yet beta thalassemia's clear, easily-measurable outcomes – does a patient still need blood transfusions? – make it one of the best candidates for such a deal. Most of these arrangements are fiendishly difficult in practice. Although they are gaining traction for the most expensive therapies, they don't offer a feasible solution for all the high-priced orphans coming down the pipe. Reliably measuring outcomes in sickle cell disease, for instance, is harder: this inherited blood disorder, which affects 100,000 Americans, has many painful symptoms and potential trial endpoints.

The growing cohort of treatments – including one from *Global Blood Therapeutics, Inc.*, acquired by *Pfizer Inc.* in August for $5.4bn—is welcome, but costly. Reimbursing cancer drugs is another worry: over 40% of all orphans approved in the last decade target rare cancers, according to *IQVIA Holdings Inc.*. And cancer treatments are increasingly used in combination, ramping up aggregate costs into the millions and having a disproportionate impact on already over-whelmed budgets. (Also see "*Pfizer's Buying Spree Continues With GBT, Gaining A Sickle Cell Disease Franchise*" - Scrip, 8 Aug, 2022.)

Show The Evidence

Outcomes deals may not offer a scalable solution to the budget challenges spurred by rare diseases treatments, but they do underline tighter payer and regulatory scrutiny of these drugs' actual performance. FDA is trying to improve its record on chasing post-marketing evidence requirements for drugs receiving Accelerated Approval based on surrogate endpoints (of which many are orphans), and for withdrawing drugs that fail to show positive results.

German authorities, also frustrated by weaker evidence behind products receiving expedited approval, in 2021 began mandating that drug-makers collect real-world data to support their drugs. Novartis' Zolgensma, conditionally approved in the EU in 2020, was first up. The Federal Joint Committee (G-BA) set out precisely what data it wanted to see, including comparators and endpoints, in a full added-benefit assessment of Zolgensma in 2027 at the latest. (Also see "*Gene Therapy Pricing To Come Under Microscope In Germany*" - Pink Sheet, 17 Nov, 2021.)

Stronger evidence will help justify rare disease drug pricing. But it also won't, on its own, address the budgetary impact of this expanding category. And the new US drug pricing laws could make the problem even worse.

US Pricing: Unintended Consequences

Most orphan drugs will be shielded from the battery of drug price-cutting measures within the US Inflation Reduction Act (IRA). From 2026, the US government-funded Medicare will negotiate prices for some top-selling drugs, with a cap on the maximum negotiated price, an excise tax on prior year sales of up to 95% for manufacturers who refuse to negotiate, plus rebates on any Medicare drugs whose prices rise faster than inflation.

Orphan drugs are unlikely to fall into the early price negotiation cohorts – the ten highest-cost out-patient administered drugs in 2026, rising to include hospital-administered products in 2028. But the IRA explicitly excludes from negotiation orphans approved for only one rare disease, and those that cost Medicare less than $200m annually. Drugs that account for more than 80% of a single company's revenues – a common scenario for rare-diseases-focused biotechs—are also protected. In sum, the law gives orphans "a bit of a pass," said ICER's Pearson.

Yet an unintended consequence of the IRA may be higher drug launch prices – including for orphans—as disgruntled manufacturers seek to squeeze as much as they can out of new products before potential negotiations kick in, and as they seek to avoid fines for above-inflation annual price rises along the way. "It's a well-intended piece of legislation that sends a message to industry," said Sherman. But the lack of any limit on launch prices "is absolutely a concern," for orphans and non-orphans. Sherman is also worried that industry, facing lower reimbursement from Medicare, may try to claw back funds by charging more to commercial insurers.

The US pharmaceutical industry lobby, PhRMA, claims the law will damage innovation, puncture company valuations, and leave dozens of drugs undeveloped, even though the new rules won't touch medicines during their market exclusivity. Negotiations will apply only to small molecules at least seven years post-launch, and to biologics at least 11 years post-launch. PhRMA's indignation may be justified over the longer term, though. Once the US government gets a taste

of the savings (more than $100bn over ten years, according to the Congressional Budget Office), it will probably come back for more. The conceptual block on a US government negotiating drug prices is removed.

In the US, orphan drug sales growth is likely to continue to outpace the wider market. Despite competition building in some rare conditions, like SMA, the blood cancer myelofibrosis, or paroxysmal nocturnal hemoglobinuria, which affects red blood cells, "most people see a future where rare diseases drugs are more plentiful and more expensive," said ICER's Pearson. FDA, in early 2022, declared its continued prioritisation of rare diseases, and further moves to accelerate approvals, including by expanding the Real Time Oncology Review program beyond cancer (it allows sponsors to submit data on a rolling basis, before full results are available.) So far this year, 11 of FDA's 19 drug approvals have orphan designation. (See Table 1.)

IRA's treatment of niche drugs could make them even more popular stateside, while tighter reimbursement rules in Europe have the opposite effect. The discrepancy is unlikely to help either continent achieve a better balance between encouraging R&D innovation and ensuring fair and appropriate access. Maybe near-term experiences in both regions will help map the unhealthy extremes, yet neither addresses the relative lack of progress in more widespread conditions like heart or kidney failure, dementia or depression.

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