

Do ultra-orphan medicinal products warrant ultra-high prices? A review

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Abstract: Ultra-orphan medicinal products (ultra-OMPs) are intended for the treatment, prevention, or diagnosis of ultra-rare diseases, ie, life-threatening or chronically debilitating diseases that affect less than one per 50,000 individuals. Recently, high prices for ultra-OMPs have given rise to debate on the sustainability and justification of these prices. The aim of this article is to review the international scientific literature on the pricing of ultra-OMPs and to provide an overview of the current knowledge on the drivers of ultra-OMP pricing. The pricing process of ultra-OMPs is a complex and nontransparent issue. Evidence in the literature seems to indicate that ultra-OMPs are priced according to rarity and what the manufacturer believes the market will bear. Additionally, there appears to be a trend between the price of an ultra-OMP and the number of available alternatives. Patients, third-party payers, and pharmaceutical companies could benefit from more transparent pricing strategies. With a view to containing health care costs, it is likely that cost-sharing strategies, such as performance-based risk sharing arrangements, will become increasingly more important. However, it is vital that any measures for price control are consistent with the intended goals of the incentives to promote the development of new OMPs. Ideally, a balance must be struck between attaining affordable prices for ultra-OMPs and securing a realistic return on investment for the pharmaceutical industry.

Keywords: ultra-orphan medicinal product, ultra-rare disease, pricing

Introduction

In the European regulation, rare diseases are described as “conditions that occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent, or treat the condition would not be recovered by the expected sales of the medicinal product.” In Europe, the maximum prevalence of a rare disease is five cases per 10,000 individuals.¹ The World Health Organization adopted a definition in which the maximum prevalence of a rare disease is 65 cases per 100,000 individuals.² Ultra-rare diseases constitute an informal subcategory, within rare diseases, to describe *very* rare diseases. The frequency of ultra-rare diseases is not well defined; consequently, no formal legal definition exists.³ The term was first used by the National Institute for Health and Care Excellence (NICE), for a rare disease affecting less than 1000 cases in England and Wales, which corresponds to a prevalence of less than one case per 50,000 individuals.^{4–8} Prior to the regulation, the ultra-orphan market was considered unattractive and unprofitable.

Recent statements seem to indicate that the tide is turning. The pharmaceutical industry, confronted with lagging traditional drug approvals and declining investments, is seeking new sources of income.^{9,10} Spurred by high prices,

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pharmaceutical companies have moved from traditional blockbusters to niche-busters.^{11,12} Shorter clinical development time, the high level of unmet medical need, and successful regulatory submissions fuelled a turn to targeted medicinal products.¹² Nowadays, orphan medicinal products (OMPs), intended for the treatment, diagnosis, or prevention of ultra-rare diseases, represent attractive investment opportunities.^{1,9,10} A few OMPs even qualify as blockbusters, as their global annual sales exceed \$1 billion.¹⁰

High prices for ultra-OMPs can be traced back to the need to recoup a high cost of research and development (R&D) from a small number of patients.¹³ Genzyme was the first to charge a high price for imiglucerase, and other ultra-OMPs soon followed.^{10,14} Imiglucerase, an enzyme replacement therapy (ERT) for the treatment of Gaucher's disease, costs between \$100,000 and \$400,000 per patient per year. Although there are only 2000 patients in the United States and 6000 patients worldwide, the revenue from imiglucerase approached US \$1.8 billion in 2009.^{10,11,15} Similarly, agalsidase beta (for the treatment of Fabry disease) and laronidase (for the treatment of mucopolysaccharidosis type I), respectively cost \$300,000 and \$350,000 per year per patient.^{11,16} In a study by Orofino, the average of the mean cost per patient across several European countries ranged from €3523 to €337,501 for 14 ultra-OMPs.¹⁷ The yearly cost of eculizumab (for the treatment of paroxysmal nocturnal hemoglobinuria) is the highest, at just under \$500,000 per patient.^{9,10} In 2010, eculizumab generated \$541 million in sales.¹² Remarkably, eculizumab was originally intended for the treatment of arthritis, and would probably have been priced in the range of similar medicinal products at \$20,000 per patient per year.¹⁸ Extraordinary price increases (defined as increases of more than 100% at a time) have also been documented when established off-label use of a medicinal product became approved.^{19,20} For example, unlicensed use of 3,4-diaminopyridine for the treatment of Lambert-Eaton myasthenic syndrome cost approximately €1000 per patient per year. The price of the marketed version is 50–70 times higher.²¹

Prices, often as high as the market will bear, have given rise to arguments on the justification of high prices.²² For example, the Dutch government questioned the high prices of some ultra-OMPs for the treatment of hereditary metabolic disorders.²³ The pricing process of ultra-OMPs has been viewed as arbitrary and nontransparent.²⁴ Additionally, there is a debate on the sustainability of high prices for ultra-OMPs within the context of current health care systems.¹²

The aim of this article is to review the international scientific literature on the pricing of ultra-OMPs. In that way, we aim to provide an overview of the current knowledge on the drivers of ultra-OMP pricing.

Methods

The literature review identified studies by searching the following databases: MEDLINE, Embase, Web of Knowledge, EconLit, National Health Service (NHS) Economic Evaluation Database, and Cochrane Database of Systematic Reviews. The following search terms and combinations thereof were used: orphan drug; orphan medicinal product; ultra-orphan drug; ultra-orphan medicinal product; rare disease; ultra-rare disease; rare disorder; ultra-rare disorder; ERT; price; pricing; policies; price-setting; market access; budget; and regulation. The last search was performed on February 28, 2013. For practical reasons, all selected studies were published in English, French, or Dutch. Bibliographies of relevant articles were searched for additional references.

The pricing process of ultra-OMPs

The pricing of ultra-OMPs has been described as complex and arbitrary.^{24,25} Recently, Michel and Toumi recognized the lack of research on the pricing of OMPs.⁶ Pharmaceutical pricing itself is not an event, but a process of value judgment in which the context is provided by an interplay of factors.²⁶ It was observed that the pricing mechanisms for OMPs are essentially similar to those for traditional medicinal products, ie, a price is initially set based on the company's profitability and return on investment and then compared to the reality of the target market.²⁷ According to Kolassa, eight factors must be considered: two *internal* factors relating to (1) company needs (ie, need to recover R&D costs) and (2) abilities; and six *external* factors: (3) value (ie, perceived medical benefit); (4) competitive environment (ie, availability and prices of alternative and competing medicinal products); (5) patient and disease characteristics (ie, disease prevalence); (6) reimbursement environment; (7) decision making; and (8) public policy environment. Factors one to four are considered the main drivers in determining price and price changes.^{24,26} In the following paragraphs, an overview will be given of these different factors relevant to pricing of ultra-OMPs.

Internal factors: company needs and company abilities

As with any medicinal product, its price is an attempt to recoup investments in R&D.¹⁷ On the one hand the development cost of an OMP, on average \$90 million,

amounts to only 25% of the cost of development of traditional medicinal products. Due to the smaller patient population, clinical trials for ultra-OMPs are much smaller and therefore likely cheaper than traditional clinical trials.^{11,28} On the other hand, the price of one ultra-OMP also factors in R&D expenditures for hundreds or thousands of compounds that failed to achieve marketing authorization. Pharmaceutical drug development is a risky process; approximately a third of all compounds fail Phase III trials.^{29,30} Over the last years, increased pipeline attrition has added to increased R&D expenditures.¹² Additionally, expensive surveillance programs are often imposed by regulatory authorities as a post marketing commitment.³¹ Miyamoto et al suggested that cost management, through increased use of surrogate endpoints and expedited review, could decrease development costs to \$28 million.²⁸ Nevertheless, development costs are still considered the highest for the rarest of diseases.² An independent study estimated the development cost of imiglucerase at less than \$30 million.²⁴ For some 'repurposed' medicines, the effectiveness evidence was published prior to the application for orphan designation. In those cases, the costs of R&D are believed to be negligible. Nevertheless, upon comparing Belgian hospital prices per defined daily dose of the medicine for the common indication versus the rare indication, up to a 200-fold price difference was reported.³² Finally, several patient advocacy groups actively fund and support clinical development. For example, the American Cystic Fibrosis Foundation has invested more than \$300 million towards the development of new treatments for cystic fibrosis.¹¹

Worldwide, legislation is in place to stimulate the development of OMPs. Incentives include free protocol assistance, fee reductions, tax credits, expedited review by registration authorities, and granting a period of marketing exclusivity.^{1,33} In Europe, the overall fee reductions for all OMPs amounted to €6,840,900 in 2005.⁶ These incentives increase the commercial value of OMPs by reducing R&D expenses and shortening time-to-market.^{19,34} Despite these incentives to promote the development of OMPs, there is no guarantee that an OMP will become available or remain available on the market.¹⁵

Many ultra-OMPs are biotechnological products, manufactured through complex and expensive processes.¹⁴ The high cost of acquiring and/or manufacturing the active ingredient is often put forward to justify the price of an OMP.¹¹ Nonetheless, production costs and molecular complexity do not seem to correlate with the prices of OMPs. After all, changes and advances in the production method of imiglucerase for Gaucher's disease did not lead to a reduc-

tion in price. Monoclonal antibodies, of similar molecular and manufacturing complexity, are sold at far lower or far higher prices.²⁴

At the same time, opportunities arise when marketing in small target populations. The costs associated with the sale of OMPs are low.¹¹ There are indeed some extra costs associated with setup, such as building referral networks, training physicians, and supporting patient advocacy groups,² however, marketing costs are lowered by using social media for direct-to-patient advertising through patient advocacy groups.^{10,11}

Finally, market exclusivity and/or patent protection also enable the marketing authorization holder to set a high price. Additionally, there is no oversight body to control prices.^{19,24} Corporate strategy with respect to pricing ultra-OMPs can therefore be summarized as setting the price as high as the market will bear.^{19,22}

External factor: value

The concept of value or therapeutic benefit is dependent on factors such as seriousness of condition, level of unmet needs, and incremental clinical benefit.²⁶ By definition, rare diseases are life-threatening or serious chronically debilitating diseases for which no or few alternative treatments are available.¹ The level of incremental clinical benefit, however, is usually not fully established when the price is set. In most cases there is limited information on the natural course of an ultra-rare disease. Additionally, in small populations, difficulties in generating evidence to demonstrate clinical benefit arise. Roos et al claim that the therapeutic benefit of an OMP does not correlate with its price.²⁴

External factor: competitive environment

Competition during the period of market exclusivity

During the period of market exclusivity, no *similar* product can be marketed for the same indication.^{6,10,31} The first applicant can lose market exclusivity to the benefit of the second, if the second product is superior in terms of safety or efficacy.⁶ Sponsors of dissimilar products can apply for a separate marketing authorization, but are often discouraged from doing so by the small target population and high costs.^{2,6} In one exceptional case, agalsidase beta and agalsidase alfa were both approved in Europe, through a whim of administrative flexibility, for the treatment of Fabry disease.¹⁵ For some of the most common rare diseases, such as pulmonary arterial hypertension, up to four different OMPs are available on the European market. By contrast, the very small size of the target population brings about little competition in the

field of ultra-rare diseases.^{2,9,35,36} Nevertheless, premium prices have attracted some competition, even in very small markets. For example, in the United States, both imiglucerase and taliglucerase alfa are available for the treatment of Gaucher's disease.¹⁰

In some cases, a monopolistic situation is created in which only one medicinal product is available for a single indication, spurring manufacturers to dictate high prices.^{6,10,19} However, results on that issue contradict each other; only a trend that is not significant has been reported between the number of available alternatives for a rare disease and the price of OMPs.²⁵ Furthermore, an analysis investigated the influence of awarding orphan designation status (and thus market exclusivity at the time of marketing authorization) on the price setting of medicines for rare indications. Upon comparing Belgian hospital prices per defined daily dose of 28 designated OMPs and 16 comparable non-designated medicines for rare disease, a significantly higher median price was recorded for the former (€138.56) compared to the latter (€16.55).³⁷ In contrast, no statistically significant difference in price distribution was found between French hospital prices of 41 medicines with, and 17 medicines without, orphan designation.³⁸ On that account, market exclusivity and lack of alternatives are likely associated with higher prices for medicinal products for rare diseases, but not as the only sources of higher prices.^{37,38} Article 8.2 of the regulation on OMPs allows for the period of market exclusivity to be reduced to six years.¹ Member States can invoke the application of this procedure for a highly profitable OMP with a view to lowering its price. At that point however, immediate price decreases due to direct competition are unlikely.³⁹

Competition from generic medicinal products

Competition from generic medicinal products can only occur when all protection on the originator medicine has elapsed.⁴⁰ Besides patent protection, OMPs also benefit from a period of market exclusivity. Market exclusivity may give exclusivity beyond the patent, therefore sustaining return on investment after patent expiration.³⁶ Even if the period of market exclusivity is reduced, most medicines will still be protected by patents.⁴¹ In Europe several OMPs (imatinib, bosentan) have lost or will soon lose both their market exclusivity and patent protection.⁴² Recently, the Committee for Medicinal Products for Human Use adopted a positive opinion on marketing authorization for a generic version of imatinib.⁴³ Potential price decreases, due to entry of generic OMPs, are difficult to predict.⁴² Prices of

traditional generic medicines tend to be 10%–80% lower than those of originator medicines.⁴⁴ In the US, generic prices of a sample of 12 OMPs were on average 50% lower than the original medicine.⁴² Biosimilars could be sold at a price 10%–30% lower than the originator.⁴⁵ However, the biosimilar velaglucerase alfa is priced higher than the originator imiglucerase. It is also likely that competing manufacturers, in order to maximize their own revenue, will set their price just below the price of the originator medicine. Estimates show that at least five competitors are needed to achieve significant price reductions, an unlikely scenario in the ultra-OMP market.^{24,41}

On that account, it remains to be seen whether competition in the field, from other OMPs or generic versions, can lead to price reductions and savings in the health care budget. Nevertheless, competition may stimulate future innovation and could help in reducing critical supply shortages of life-saving medicines.⁴⁵

External factor: patient and disease characteristics

Because ultra-OMPs target small populations, high prices are needed to recoup (volume-independent) R&D expenditures.^{6,13} As such, there is an inverse correlation between the price per capita of an ultra-OMP and the prevalence of the disease; the rarer the disease, the more expensive the treatment. In other words, the yearly cost per patient is inversely related to the prevalence of the disease.^{25,27,31,46} The inverse relationship, however, is not linear and there are exceptions; some prices of medicinal products, with similar prevalence, differ as much as sevenfold.²⁴

The first symptoms of an ultra-rare disease usually occur during childhood.¹⁴ For example, Fabry disease is characterized by an accumulation of a glycolipid within various organs, leading to severe manifestations starting in early childhood. Therefore, some ultra-orphan lysosomal storage disorders often require life-long ERTs.⁷ In the case of ERTs, the cost of treatment also directly relates to the dose of the treatment.¹⁵ Thus far, the cost-effectiveness of lower dosages has not been established and, therefore, the optimal price is not known. On the other hand, ERTs also generate some (marginal) savings, as patients may require less or no symptomatic care.¹⁴

Evidence also shows that the price of an ultra-OMP is set according to the prevalence of a single, ie, the initial, indication.⁴⁷ Indeed, companies are encouraged to develop a medicinal product for a rare indication and promote its use. Thereafter, new indications are sought and the OMP is

marketed at the high initial price, generating disproportionate returns.^{11,47} For some OMPs, the target population is broad; for example, imatinib is now used for both orphan as well as non-orphan oncolytic indications.^{10,31} In a study by Kesselheim et al, statistically significant non-orphan and off-label use was found in three of four top-selling OMPs studied.⁴⁸ Nonetheless, (off-label) expansion is unusual for ultra-OMPs, as these therapies mostly target disease-specific pathways.²

In a study by Aballea, the association between several disease-related and drug-related variables and the prices of 51 OMPs in five European countries was studied using regression analysis. However, no significant association was found between any of the disease-specific variables (disease area, prognosis, age and vulnerability of target population, seriousness, number of available treatments, and course of illness) or drug-specific variables (year of approval, trial size, number of trials, comparator in trial, Anatomical Therapeutic Chemical Classification System [ATC] code, evidence of benefit) and price. A not statistically significant association was found between high prices and low prevalence and low number of treatment alternatives.²⁵

External factor: reimbursement environment

In most European countries, ultra-OMPs are fully reimbursed, whereas in the United States and Canada copayments for patients exist.^{6,49} As such, high prices for ultra-OMPs have a direct (through high financial costs) and/or indirect (through the fear of having funding for the treatment withdrawn) effect on patient access.²⁴ Patients can get access to ultra-OMPs via health insurance or alternatively through company funded patient assistance programs.¹⁰

The reimbursement of ultra-OMPs can create conflicts between the rights of individuals (ie, right of access to treatment) and overall health of a society. On the one hand, the principles of equity and no abandonment imply that treatments for life-threatening diseases should be made available, regardless of their cost. The fact that for most ultra-rare disease no alternative treatment is available also underlines the high therapeutic need.⁵⁰ On the other hand, society allocates health budget to interventions with a view to maximizing the health of the population as a whole. As such, reimbursement of expensive ultra-OMPs for a minority of patients brings about missed opportunities in treating common illnesses with inexpensive medicinal products.^{4,16,51} Ideally, reimbursement decisions should reflect public preferences, but at the moment, preference towards reimbursement

of ultra-OMPs is not fully evident.⁵² Moreover, in times of economic hardship, there is increasing pressure to contain health care costs.

Ultra-OMPs are seldom cost-effective, on the one hand due to their high price, and on the other hand because of the uncertainty surrounding the long-term effectiveness and clinical benefit.^{4,5,14} Consequently, ultra-OMPs are expensive per unit of healthy life years gained.²⁰ If they are judged against traditional thresholds, ultra-OMPs are unlikely to meet them.^{11,35} The probability even declines with decreasing prevalence.^{35,53} Nevertheless, the willingness-to-pay for ultra-OMPs by patients, the population, and/or third party payers is high; on the one hand, this is because of the seriousness of the disease and the lack of suitable alternatives, and on the other hand, because one can easily identify with ultra-rare disease patients.^{11,19} Evidence indicates that the public prefers to offer treatments to those with the worst initial health state, even if this is not a cost-effective allocation of resources.¹³ The majority of 27 participants of the Citizen's Council set up by NICE in England and Wales voted to pay premium prices for medicines to treat very rare conditions.^{7,14} Because of the low impact on the budget of the NHS, NICE does not evaluate ultra-OMPs. Recently, a new Advisory Group for National Specialized Services was created, with a mandate to work out a new system to assess highly specialized services such as ultra-OMPs. The assessment consists of a two-stage procedure, where the suitability of the drug for national commissioning is verified in the first stage, and the drug is assessed in the second phase against 12 criteria that belong to the four groups of health gain, societal value, reasonable cost, and best clinical practice.⁵⁴ As such, this is an application of multi-criteria decision analysis, an assessment system based on weighted evaluation criteria. An innovative assessment system for OMPs based on several weighted evaluation criteria (eg, severity, disease severity) has been proposed by Hughes-Wilson et al. If in fact society reveals a preference in treating ultra-rare diseases, multi-criteria decision analysis allows decision-makers to evaluate treatments based on a predefined ranking system.³⁵ An ethical framework has also been proposed in which a fair share of health care resources are allocated to rare diseases. The model is based both on budgetary insulation, which allows access to treatment for certain patients, and on possible access for a few randomly selected patients.⁵⁵

External factor: decision making and public policy

At present, regulatory restrictions and procedures for pricing and reimbursement vary in each country; therefore, prices

for ultra-OMPs vary from one country to another.^{27,56} For example, Eastern European countries may have the highest prices (based on purchasing power) according to one study.⁴⁹ Pharmaceutical companies often opt to market new medicinal products first in countries with free-pricing systems, such as Germany.^{24,41} It is however also possible to set high prices in some countries where pricing is more restricted (ie, Portugal, Spain). For example, in France a system of Temporary Authorization for Use (ATU) exists to make a medicinal product available and fully reimbursed before marketing authorization. The price and indication during the time of ATU should ideally reflect future authorized indications and price.⁵⁷ However, some manufacturers are inclined to set a high price in the ATU system, in an (usually successful) attempt to retain high price after marketing authorization.^{24,41}

Local pricing and reimbursement policies do not always align with wishes of patients, society, and pharmaceutical companies. For example, the logic of cost-effectiveness applied by third-party payers conflicts with the needs of ultra-rare disease patients for speedy access to treatment.^{13,19} Additionally, there is often pressure from patient organizations and society to provide treatments.²⁴ In that debate, pharmaceutical companies highlight the (perception) of unmet need and the well-being of patients.^{20,25} From a point of view of the pharmaceutical industry, it also appears as if third-party payers are much too focused on containing health care costs, and in that way are unwilling to reward pharmaceutical innovation.⁵⁶

Third-party payers are increasingly concerned with escalating health care costs.⁴⁵ Prices for ultra-OMPs are high, and the system of third-party payers provides limited incentives for physicians and patients to be cost-conscious.^{19,58} Although ultra-OMPs are expensive per patient, overall drug expenditure is expected to be limited because of the narrowness of the market.^{20,27} However, when combined, a large number of patients can still have a large impact on health care budgets.^{3,7} A Belgian study showed that the impact of OMPs is substantial, ie, amounting to 1.9% of pharmaceutical expenditure in 2008. All three growth scenarios predicted a significant rise in expenditure in the future.⁵⁹ Orofino et al anticipated that, although expenditure in OMPs will continue to increase, it will remain a low percentage of overall pharmaceutical expenditure.¹⁷ The most recent analysis by Schey et al predicted that the expenditure on OMPs, as a proportion of total pharmaceutical expenditure, is likely to plateau between 4%–5%.⁴² To date, no specific data estimating the budget impact of ultra-OMPs are available to the best of the authors' knowledge.

At the moment, European member states have the responsibility to revise pricing for ultra-OMPs, but they often have limited power to negotiate lower prices.^{6,24} For example, in France, treatments for Fabry diseases are procured under special programs, of which the details are unavailable to the public.⁴⁹ Prices of OMPs that are distributed through the hospital pharmacy can also be negotiated between the manufacturer and the hospitals.³¹ In some cases, (virtual) centers of expertise for ultra-rare diseases can also attempt to purchase ultra-OMPs at a lower price.³ For example, through direct purchases of ultra-OMPs from the manufacturer or supplier, commercial discounts (such as price reductions), rebates, or in some cases cost-free products, can be obtained.⁶⁰

Sustainability and ways forward

High prices for ultra-OMPs have a negative effect on the pharmaceutical industry's reputation, as the general population considers it indecent to profit from the misfortunes of others.^{19,58} But the expectations of the general public are at odds with itself; on the one hand they expect the industry to develop new life-saving medicines, on the other hand there is a taboo against commercialization and profit seeking in health care.⁵⁸

Pricing of ultra-OMPs is an important and delicate issue as it has a direct effect on patient access to health care.¹⁹ While there may be benefits for patients, high prices fuel the demand for price controls. However, without appropriate benchmarks, it is difficult to assess whether the price of an ultra-OMP is too high or too low relative to its value.⁴⁷ Revenue is approximated by multiplying market size and the price of a medicinal product; however, market size is only roughly estimated, as there are few reliable data on prevalence of ultra-rare diseases.²⁸ Consequently, it is equally difficult to calculate the profitability of an ultra-OMP, roughly defined as what a company gains of benefit from one product, especially if there is more than one indication.^{39,41} The industry would benefit from appropriate benchmarks and a clear definition of profitability.⁴⁷ In Japan, companies with profitable OMPs (ie, with annual profits over JPY 100 million) pay a 1% tax on sales with a view to repaying received benefits.⁶¹

European member states also have a different ability to pay for high-priced ultra-OMPs. Differential pricing is an instrument according to which a pharmaceutical manufacturer establishes a higher price for the drug in a more affluent country, but accepts a lower drug price in a country where consumer demand is more responsive to price changes.⁶² The application of differential pricing to ultra-OMPs may enhance

equality of access to these innovative pharmaceuticals for unmet medical needs across Europe.

According to McCabe et al, there is also scope for price negotiations, for example, by refusing to pay exorbitant prices or by making demands on discounts.^{9,63} However, these price controls need to be consistent with the intended goals of the incentives to promote the development of new OMPs.¹⁹ Price controls create short-term benefits, but they could also create shortages and could take away incentives to invest in the development of new OMPs.¹⁹

The uncertainty of the cost-effectiveness often hampers timely access to new ultra-OMPs. New market access agreements, such as performance-based risk sharing arrangements, offer a unique way to dealing with the unproven long-term effectiveness of expensive ultra-OMPs.⁵³ If after a certain period of time the clinical evidence is not sufficiently convincing, a decrease in price can be considered.^{47,64} In February 2013, there were eight OMPs with approved Patient Access Schemes and recommended by NICE for use in the NHS.⁶⁵ Although experience of employing new market access agreements in the field of ultra-rare disease is still limited, it is likely that these strategies will become increasingly more important. Nonetheless, it is vital to safeguard transparency on funding, privacy, patient selection, and governance.⁶⁶ For example, new market access agreements based on effectiveness for the treatment of mucopolysaccharidosis IV, an ultra-rare disease, were found to be potentially disadvantageous for slowly progressive patients.¹³ Agreements must also allow for flexibility; as the therapeutic context may evolve over time, it is vital to continuously match the research design to current uncertainties.^{67,68} Alas, new market access agreements are also costly; there are considerable costs associated with monitoring, negotiation, and evaluation. From a societal point of view, new market access agreements can be considered as an investment in data collection to inform pricing arrangements.⁶⁸

Conclusion

A lot of vagueness still surrounds the pricing mechanisms for ultra-OMPs. The literature appears to indicate that ultra-OMPs are priced according to rarity and what the manufacturer believes the market will bear. Patients, third-party payers, and pharmaceutical companies could benefit from more transparent pricing strategies. Therefore, future research should continue to focus on the different factors that influence pricing of ultra-OMPs. Ideally, a balance must be struck between attaining affordable prices for ultra-OMPs and securing a realistic return on investment for the pharmaceutical industry.

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