Reimbursed Price of Orphan Drugs: Current Strategies and Potential Improvements

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Abstract

The pricing and reimbursement policies for pharmaceuticals are relevant to balance timely and equitable access for all patients, financial sustainability, and reward for valuable innovation. The proliferation of high-cost specialty medicines is particularly true in rare diseases (RDs) where the pricing mechanism is characterised by a lack of transparency. This work provides an overall picture of current strategies for the definition of the reimbursed prices of orphan drugs (ODs) and highlights some potential improvements. Current strategies and suggestions are presented along 4 dimensions: (1) comprehensive value assessment, (2) early dialogs among relevant stakeholders, (3) innovative reimbursement approaches, and (4) societal participation in pro-

ducing ODs. Comprehensive value assessment could be achieved by clarifying the approach of distributive justice to adopt, ensuring a representative participation of stakeholders, and with a broad consideration of value-bearing factors. With respect to early dialogs, cross-border cooperation can be determinant to companies and agencies. The cost-benefit ratio of early dialogs needs to be demonstrated and the “regulatory capture” effect should be monitored. Innovative reimbursement approaches were developed to balance the need for evidence-based decisions with the timely access to innovative drugs. The societal participation in producing ODs needs to be recognised in a collaborating framework where adaptive agreements can be developed with mutual satisfaction. Such agreements could also impact on coverage and reimbursement decisions as additional elements for the determination of a comprehensive societal value of

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ODs. Further research is needed to investigate the highlighted open challenges so that RDs will not remain, in practical terms, orphan diseases.

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Introduction

Across the countries belonging to the Organisation for Economic Co-operation and Development (OECD), pharmaceutical spending in 2013 reached almost 20% of total health spending on average, equivalent to 1.4% of gross domestic product [1]. As reported in that OECD report, the proliferation of high-cost medicines is expected to be a major driver of health spending growth in the coming years, although some of these new medicines provide only marginal health benefits [1]. In this context, pricing and reimbursement policies are relevant to ensure a balance among timely and equitable access for patients, financial sustainability of publicly funded health systems, and valuing of industrial innovation [2, 3]. High prices are observed in therapeutic areas such as cancer, multiple sclerosis, pulmonary disease, hepatitis C, rheumatic diseases, and rare and ultra-rare diseases [1]. In the specific case of orphan drugs (ODs), while regulations have stimulated research and development of orphan medicinal products [4], equitable and timely access to approved ODs for rare diseases (RDs) remains an issue, and effective market access and utilisation vary strongly between and within states [5, 6]. Additionally, the OD market share for non-generic prescription drugs is expected to increase worldwide from 13.8% in 2013 to 20.2% in 2020 [7]. The pricing mechanism for ODs is characterised by a lack of transparency [6, 8, 9]. Up to now, only few descriptive studies have identified some factors characterising ODs' price setting, including (1) the low prevalence of the indication [10], (2) the uncertainties in reaching the expected number of patients [11], (3) the expensive surveillance programmes imposed by regulatory authorities for fast-tracked to market ODs [12], and (4) the absence of alternative treatments [8].

From a pragmatic perspective, the reimbursed price of drugs results from a negotiation between a pharmaceutical company and the representatives of national health authorities. Pharmaceutical companies often work in monopolistic conditions, especially during the period of market exclusivity [6, 13–15]. Besides the limited availability of specific information, third-party payer organisations are under pressure from patient advocacy groups and mass media [12], especially in present times

where the financial crisis forces governments to apply pricing and reimbursement control measures. These cost containment measures may undermine the continued provision of equitable and comprehensive healthcare for the population as well as health outcomes such as health expectancy and health-related quality of life [16]. In this scenario, value-based pricing plays an important role.

Across national public health systems, well-defined processes are in place to support decision makers in setting value for money of new health technologies [17] coming into the market. Health technology assessment (HTA) [18], as described by Lampe et al. [19], is intended to identify, appraise, and synthesise all available scientific evidence to inform decisions considering 10 different domains: characterisation of the specific health problem and existing current treatment alternatives; description of the technology under scrutiny; evidence on safety, clinical effectiveness (comparative effectiveness), and cost-effectiveness; budget impact analysis; ethical analysis; and considerations of organisational, social, and legal issues. In the case of ODs, several of the above-reported domains become critical [9, 12, 20–25], feeding an open worldwide debate about the appropriateness of existing HTA methods for health technologies devoted to RDs [26–29]. Increasingly, considerations of using an extended set of criteria beyond the conventional core assessment of safety, efficacy, and cost-effectiveness is gaining acceptance even among the HTA community [30–32].

The aim of this paper was to provide an overall picture of current strategies for the definition of the reimbursed prices of ODs, identifying current strategies and potential improvements.

Discussion

Reimbursed Price of ODs: Current Strategies and Potential Improvements

The current strategies for OD reimbursement are classified according to a conceptual framework with 4 dimensions (Fig. 1): (1) comprehensive value assessment, (2) early dialogs among relevant stakeholders (i.e., before phase III clinical trial), (3) innovative reimbursement approaches to allow timely access to ODs, and (4) societal participation in producing ODs.

Comprehensive Value Assessment

Current discussions on financing ODs deal with principles of priority setting based on distributive justice, involvement of stakeholders along the evaluation process,

Fig. 1. Conceptual framework for analysing current strategies for pricing definition.

and value-bearing factors and their combination for a comprehensive assessment [22, 33–35].

Priority setting involves complex value-laden choices that are often socially, ethically, and politically controversial, implying opposite interests for different stakeholders, including government officials, pharmaceutical companies, patient, and the public [22]. Two main and contrasting principles can be distinguished: the utilitarian approach (i.e., healthcare resources are distributed so as to achieve maximum “benefit” in terms of population health), and the rule of rescue (i.e., resources are only assigned to satisfy the needs of identifiable groups in serious danger). These 2 principles could converge under a third egalitarian principle of distributive justice focused on reducing “inequalities” among groups [36]. The vulnerability of small patient groups affected by RDs with limited treatment options, commonly supported by incomplete evidence and the uncertainty for ODs in obtaining reasonable returns from industrial investments, might raise the relevance of this third principle of distributive justice [37, 38].

Two central components of a legitimate and fair distributive or priority setting process are transparency and stakeholder participation in decision-making [39]. As underlined by Douglas et al. [40], reimbursement decision-making for ODs could benefit from public and patient involvement in the following 3 different types of procedures: HTA, priority setting to address public funding, and development of evaluation criteria. As recognised by Drummond et al. [21], patients could provide valuable information on the satisfaction and acceptability of health technologies and could inform decisions supported from their values, needs, and preferences. The interaction of increased transparency in public health policies, together with the recognition of the value of the patients’ experiential expertise, could play a role in involving

public/patient representatives in coverage decision-making, either directly or indirectly by means of setting and weighing specific criteria to support coverage decision-making [21, 40].

Although there is agreement in considering a broader approach to set the value of pharmaceuticals in general, including their societal value, and regardless of some pilot experiences which are currently under development, there is no internationally agreed-on taxonomy for value-bearing criteria or measuring instruments [26, 32, 33, 41–43]. Despite these limited advances, different factors have been considered for value-bearing pharmaceuticals, including the disease and patient characteristics, the possibility of improvement either in health (effect size for efficacy and safety) or non-health outcomes (procedural attributes) [44], and the increasingly recognised value of innovation [45, 46]. Though some other issues could be considered in the specific field of RDs and ODs – such as rarity and disease severity, lack of suitable treatment alternatives, evidence of efficacy and safety, degree of product innovation, societal therapeutic impact, and potential drug use for more than 1 indication –, they are not consistently used in value assessments for coverage decisions of ODs [26, 32, 42, 47, 48].

A taxonomy of approaches to value-based pricing, spanning elements of value, measuring techniques, and aggregating approaches, has been proposed by Sussex et al. [45], who also piloted an application of multi-criteria decision analysis (MCDA) for assessing potential public reimbursement and valuing ODs. They concluded that, given the intrinsically complex nature of the RD and OD environment, an MCDA approach has the merit of ensuring transparency, reproducibility, participation, and a shared understanding of all the elements of value, with the possibility of balancing the trade-offs between them. Also, the World Health Organization (WHO) recognises

MCDA as a more holistic approach to assess the overall value of medicines under a wider spectrum of stakeholder participation, with the aim of balancing different and potentially opposing interests [49]. In 2014, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) established an Emerging Good Practices Task Force to standardise MCDA use to assess potential public reimbursement of drugs. To date, the task force has produced 2 reports: the first one defines MCDA, providing an overview of the main alternative methods and steps with examples for its use in healthcare [50]. The second report provides emerging good practice recommendations to guide the implementation of MCDA to support health policy decisions [51].

However, current funding recommendations from most HTA agencies are still mainly based on the incremental cost-effectiveness ratio – the incremental cost per quality-adjusted life year gained by treated patient. As Thokala and Duenas pointed out in 2012 [52], even though HTA agencies occasionally consider other criteria, such as severity and life-saving together with incremental cost-effectiveness ratios, there is concern that this approach may fail to capture other important sources of value. A paper recently published by Kanters et al. [53], focused on Pompe disease, illustrates the great variability in reimbursement decisions of ODs between European countries. As these authors state, it is not possible to know “how much the differences in reimbursement decisions between countries result from differences in the assessment and appraisal phase,” calling for more transparency and reproducibility in decision-making. Supporters of these changes argue that although the adoption and funding decisions of ODs are complex and multidimensional, the criteria used are unknown, inconsistently applied, and involve value judgments. Consequently, some HTA agencies are considering MCDA to manage participation of a variety of stakeholders with different interests and values, according to a more explicit and rational, participative, reproducible, and transparent framework to inform decisions [52, 54]. To that end, the European Union Committee of Experts on Rare Diseases (EUCERD) gave clear indications to the European network for Health Technology Assessment (EUnetHTA) to involve patients, clinicians, researchers, and industry representatives in the process of reviewing and adapting the assessment methods described in the network Core Model® [19, 55], specifically for ODs [5]. Under these common European methodological recommendations, national agencies could shape their final decisions based on local specificities (disease incidence and prevalence, severity,

treatment patterns, drug prices, absolute and relative treatment costs, budget impact, and/or cost-effectiveness). Other methodological issues should be considered in the specific field of RDs and ODs, such as the use of evidence provided by real-world data [31], the acceptance of intermediate or surrogate outcomes, and the adoption of off-label drugs or best supportive care as comparators. Different authors analysed possible barriers and critical success factors for the implementation of cross-border assessments in Europe and reported that autonomy in decision-making of healthcare coverage is a politically sensitive issue [56, 57]. Some of the identified success factors include the early agreement on topic selection and scope definition for assessment, a methodological framework flexible enough to fit demands/capacities from individual countries, voluntary use at the national level of the common assessment framework, the necessity to build trust among participating countries, and the need of relying on transparent and high-quality processes to get valid outputs.

Early Dialogs

A critical element of uncertainty is represented by the amount and quality of information provided by the pharmaceutical company both to HTA agencies and health authorities when dealing with assessment and pricing activities, respectively. A current challenge is to set adequate alternatives and procedures for information exchanging on study design, selection of outcome measures, and measurement instruments from earlier stages of research and development of drugs (i.e., before phase III clinical trials) [58]. Current efforts are implemented by regulatory, HTA, and/or coverage bodies to look for shared common objectives with the industry, providing scientific advice and anticipating information on procedures, requirements, and plans, and aligning time frames and other logistical aspects of the review processes [59–66]. In this contest, for example, the EuroScan International Network supports the early dialog between manufacturers, evaluators, and health services by identifying technologies and their developers before evidence has been generated [67]. In the specific case of ODs, EUCERD promoted the use of early dialogs between the industry, the European Medicines Agency, and EUnetHTA members/HTA bodies, with particular emphasis on anticipating requirements and developing a continuum and easy interactions between HTA processes and regulatory issues [5]. Despite the growing consensus, uncertainty remains on the real value of these strategies to improve patients' health expectations in a sustainable manner for public

health services [61]. Some of the questions waiting for answer we believe to apply also to ODs are: Who should fund the human resources needed to support these long-term activities? Might the closer contact and maintained interaction between industry and regulatory/assessment bodies introduce some degree of decisional bias (increased sensitivity to the concerns of manufacturers in detriment of consumers interest – “regulatory capture”)? How should conflicting advice be dealt with (e.g., in case of tri-partite advice covering both regulatory and coverage issues) [58, 68]?

Innovative Reimbursement Approaches

Various innovative reimbursement schemes are increasingly being adopted to answer to the need of faster patient access to potentially beneficial technologies. Cost containment strategies to warrant the sustainability of publicly funded health systems, when evidence is limited and there is uncertainty at the time of market introduction, are being explored [69]. Reimbursement for ODs can be granted either under the commitment of assessing clinical performance by means of relevant health outcomes – “conditional reimbursement linked to performance” and “coverage with evidence development” – or by stemming the budget impact (financially based schemes) – “price-volume” and “per patient utilisation caps” [70–72]. These reimbursement mechanisms have been categorised as managed entry agreements (MEAs) or market access agreements [73]. While conditional reimbursement schemes linked to performance are addressed to avoid inefficient expenditure on treating individual patients who do not respond to a drug and who cannot be previously identified [6], coverage with evidence development schemes looks for new evidence to reduce uncertainty about a drug’s real-life effectiveness in a cohort of patients [72]. Financially based schemes are all forms of commercial agreements taking a variety of forms, including cost capping, utilisation capping, and free and/or discounted initiation. They aim at reducing expenditures for the healthcare payer on costly drugs without collecting real-life health data from patients [6].

Given the limited effectiveness evidence for MEAs in the real world, improvements in transparency for their rationale, objectives, scope, methods for review, information collected, criteria for ending, and results of the agreement (e.g., target expenditure/use versus achieved expenditure/use, increased level of evidence) should be encouraged [74]. Besides, as suggested by the ISPOR [72], studies on MEAs should consider the value of reduced uncertainties against additional direct costs (for the negotiation,

monitoring, and evaluation phases) and the existence of any irreversibility in the process (e.g., difficulties regarding the withdrawal of a product). In the specific field of ODs, some additional considerations should be targeted, such as development of shared patient registries to enable secondary data analysis, adaptive pathways, and cross-border data pooling in order to provide valid data not limited by sample sizes issues [69, 74, 75]. Campbell et al. [76] proposed a more comprehensive procedure, supported by tools including quality indicators, to improve the assessment and potential adoption of new medicines.

Societal Participation in Producing ODs

Beyond health authorities and the industry, other stakeholders might be considered along the process of valuing pharmaceuticals for reimbursement purposes. Besides existing healthcare and research infrastructures, physicians collaborating in clinical trials on behalf of their patients and the scientific community producing the basic knowledge on diseases, an increasingly significant role is played by individual patients who share their experiences and risk their own health by participating in research programs [35]. As pointed out by Paulden et al. [32], socioeconomic policies together with access to diagnosis and treatment facilities are key elements in the final success of coverage decision for ODs. Moreover, disease advocacy groups not only contribute to accelerate research and product development, but are generally active in informing patients about new treatments, hence contributing to decrease marketing costs [77]. All these stakeholders might be considered for participating in some stages of valuing pharmaceuticals prior to the pricing processes. Patients could adequately represent their needs if involved, through patient/parent associations, in valuing drugs and informing about price setting. To satisfy this aim, the general methodological framework suggested by Tunis and Pearson [70] should be adapted to the specificities of RDs and ODs. The support provided to the pharmaceutical companies by public institutions, from early dialogs and scientific collaborations, should be planned in advance under agreements supported by future compensations. Royalties could be granted by companies to fund/support institutions/organisations in order to compensate them for their contributions to OD development. A different but related point is the issue of access to patented knowledge generated with the support of tertiary funds (either public or from advocacy groups). As reported by Lee [78], public institutions, non-profit organisations, and disease advocacy groups are increasingly conditioning their contributions to biomedical re-

search on the beneficiary commitment of sharing the likely patented inventions for non-commercial research purposes. We suggest that those pharmaceutical companies allowing further research utilisation of patented ODs by public/non-profit research institutions get an improved valuation for public coverage and reimbursement purposes. In fact, this could be an additional criterion to consider if MCDA is used for public approval and value-based pricing.

According to O'Sullivan et al. [35], a model of reduced profitability is ethically responsible and institutionally plausible, particularly for lifelong therapies, but will require pharmaceutical companies to develop new models and educate investors about the long-term advantage of regaining public trust. Pharmaceutical companies may consider that working with reduced profitability to serve society (as can be the case for ODs) may allow them to achieve a competitive advantage in the long term if done with a strategic orientation of corporate social responsibility [79].

Conclusion

Coverage decisions for ODs are complex and subject to dynamics in several conflicting factors, such as promoting timely and equitable access for patients, cost-containment strategies to sustain public healthcare services, and rewarding innovation. We wish to stimulate the debate on a comprehensive approach in the definition of health policies for ODs. We suggest to integrate the principles of distributive justice with greater process transparency and public participation, to use multiple criteria to support analysis and pharmaceutical coverage decisions, to further explore the potential of early dialogs and inno-

vative reimbursement approaches to fully understand their benefits and costs, and to apply adaptive agreements supporting future compensations to subjects contributing to the early phases of OD development. Further research is needed to investigate the open challenges so that RDs will not remain, in practical terms, orphan diseases. Addressing the discussed topics and working on the highlighted research questions becomes even more urgent as long as the advancements in the science of genomics drive an increase in personalised medical treatments gaining a quasi-orphan status.

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Disclosure Statement

The authors declare that they have no competing interests.

Author Contributions

P. Mincarone and C.G. Leo equally contributed to the work. They conceptualised and planned the study, reviewed the literature, participated in the phase of discussion on results and proposals, and drafted the initial manuscript. S. Sabina, D. Taruscio, A. Sarriá-Santamera, and P. Serrano-Aguilar participated in the conceptualisation of the study and in the phase of discussion and critically reviewed the manuscript. P. Kanavos critically reviewed the planning of the study, participated in the discussion, and critically reviewed the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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