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REVIEW

The implementation of health technology assessment principles in public decisions concerning orphan drugs

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Abstract

Purpose Over the last few years, the share of public spending for orphan drugs (ODs) has increased in several western countries, raising concern on the exemptions granted to this sector with respect to the implementation of health technology assessment (HTA) principles. The aim of this paper is to shed light on both the HTA criteria adopted and the international agreements implemented in the OD regulation, given the new challenges imposed on western countries by a growing number of therapies for rare diseases.

Methods We carried out a literature review to analyse the development of the international debate on the adaptability of HTA criteria for the OD assessment and regulation. The time span lies between January 1990 and May 2018, and the policies considered relate to both market authorization and reimbursement decisions within western countries. We focus specifically on HTA criteria in some of the dimensions included in the *Core Model* of the European net for HTA (EUnetHTA).

Results OD high prices, the absence of clarity on the possible high revenues realized by the distribution of a new OD outside the national borders, the risk that – once marketed – a new OD can be used to treat common diseases, are all issues that raise concern on OD regulation and have to be carefully monitored by policymakers in the next future.

Conclusions Across western countries, the preferential track granted to ODs in the implementation of HTA principles is not homogeneous, but fragmented and differentiated. The need for common rules at an international level is underlined, with a view to assessing the sustainability of a sector which, due to this regulatory void, can lend itself to producers' strategic and opportunistic behaviours.

Keywords Rare disease · Orphan drug regulation · Orphan drug policies · Health technology assessment

Introduction

Over the last decades, orphan drugs (ODs) have been paid increasing attention in pharmaceutical policies. On the regulatory level, both the USA with the *Orphan Drug Act* (1983) and the European Union with the *Regulation on Orphan Medicines* (2000) ruled this sector and, after the implementation of their own Directives within their boundaries, placed on the market 420[1] and 142 ODs, respectively [1, 2].

Considering the high per capita costs related to ODs, the increase in their number raises public finance problems for countries with a National Health Service [3–5]. Although in countries with public healthcare systems, the decisions on drugs' reimbursement are based on internationally shared HTA principles (see, for Europe, the European Network of HTA (EUnetHTA) and the European Medicines Agency (EMA)), the orphan drug status provides for some exemptions. As benefits include few individuals and costs are high, the implementation of cost-effectiveness principles runs the risk of excluding from treatment patients affected by rare diseases [6]. This reason, together with the difficulty in providing

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empirical evidence, has led to several exceptions in the application of HTA principles. As a matter of fact, ODs are subject to a separate regulation, both for their production, which is supported by government funding, and for reimbursement criteria.

The low profitability of these products in the internal market has pushed western countries to subsidize OD production, with a view to ensuring treatment to patients affected by rare diseases. The European Union provides both technical and tax support to companies investing in R&D on a new OD, and it also secures exclusivity on the market for 10 years[2] [7–9]. For reimbursement decisions, HTA criteria used for common drugs are partly modified to overcome the limits related to the OD status. The first limit relates to the trade-off between cost-effectiveness criteria and equity issues: On one hand, budget constraints clash with the very high per capita costs due to the limited use of ODs by general population (around 40 to 50 individuals over 100,000); on the other hand, equity principles require that each individual accesses pharmaceutical treatments that either improve his quality of life or increase his life expectancy. The second limit is more technical and deals with the difficulty of producing empirical evidence on treatments that involve a very low number of patients [1, 7, 10].

Exemptions to HTA principles have been addressed to an increased number of ODs traded in the western world over the last two decades. However, the high per capita costs are raising public finance sustainability problems leading to some considerations on the criteria that policymakers must adopt for the approval, trade and reimbursement of new ODs [11].

The aim of this paper is to shed light on both the criteria adopted and the international agreements implemented in the OD regulation, given the new challenges imposed on western countries by a growing number of therapies for rare diseases [5]. Through a literature review, we analyse the development of the international debate on the adaptability of HTA criteria for the OD assessment. The time span lies between January 1990 and May 2018, and the policies considered relate to both market authorization and reimbursement decisions within western countries.

We focus specifically on HTA criteria in some of the dimensions included in the *Core Model* of the European net for HTA (EUnetHTA) [12]. The selected domains are safety, clinical effectiveness, costs and economic evaluation, ethical issues and organizational aspects. We decided to exclude "legal aspects" and "patients and social aspects" because the former is very country-specific and the latter is not yet well documented by the international literature on ODs.

For the selected dimensions, "safety" describes the direct and indirect harms of a technology for patients, "clinical effectiveness" illustrates the spectrum and amount of beneficial health effects that is expected through the use of the technology, "costs and economic evaluation" is aimed at assessing costs, health-related outcomes and economic efficiency. "Ethical issues" consider prevalent social and moral norms relevant for the technology, while "organizational aspects" span across different issues which deal mainly with either the budget impact of the new treatment or the stakeholders involved in both the approval and distribution process of the product.

Materials and methods

The design of this study is driven by a previous literature review by Paulden et al. [5], which considers the articles published in the period between January 1990 and October 2013. We decided to make an integration to Paulden et al.'s publication, by including the literature produced between October 2013 and May 2018.

A search on PubMed and Google Scholar employing search strings – *orphan drugs policy*, *decision-making*, *orphan drugs*, *budget impact* and *orphan drug reimbursability* – was carried out. Studies were selected primarily according to the consistency of the research methods used: we privileged articles providing strong empirical evidence and/or articles addressing OD regulation with recent and valuable normative references. For the grey literature, we consulted the main sites of national and international agencies and associations (EMA, EUnetHTA, EURORDIS (Rare Diseases Europe)) that deal – although not exclusively – with the OD recognition and evaluation. Furthermore, some references were obtained directly from the reference list of the selected publications.

Figure 1 summarizes the process of identification and selection of articles through the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13]. PubMed allowed the identification of 24 articles, while Google Scholar (with the same strings) provided other 16 publications, for a total of 40 papers. Twelve of them were excluded due to their lack of relevance, and 26 were selected for full reading, after which other 11 articles were eliminated, because either they did not fit within the selected domains or they were not relevant to the scope of the present article. Ultimately, the additional studies included in this review are 17, but we also decided to re-examine 35 of the 70 works selected by Paulden et al. to deepen the analysis of their content. In selecting Paulden's articles, we adopted the criteria used for the original articles. The total number of articles considered in the present review is, therefore, equal to 52.

[2] In the USA, this guarantee is limited to 7 years.

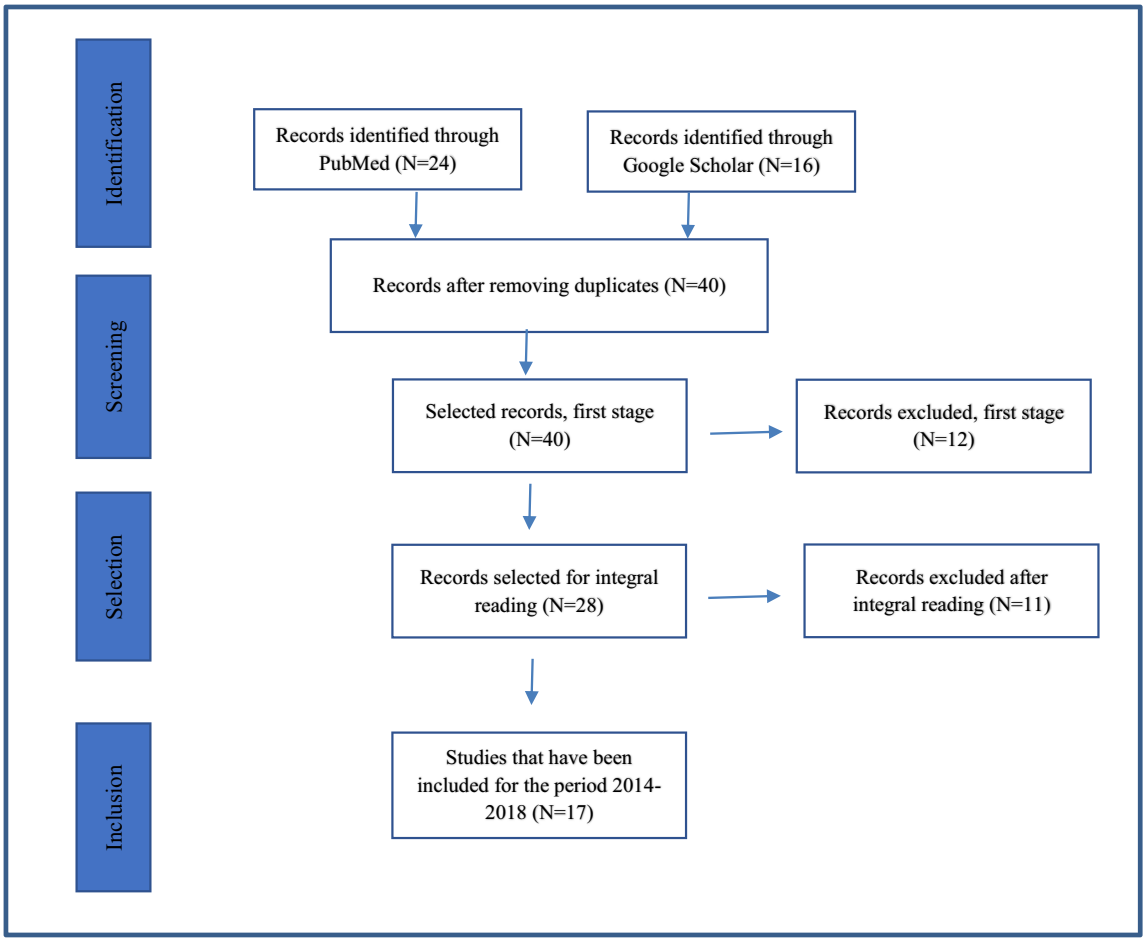

Fig. 1 PRISMA – selection of articles for the 2014–2018 period

Selected domains

Each of the following sections addresses a specific domain. A table summarizing all the findings related to each domain is enclosed in the "Appendix".

Safety

When considering ODs, safety is negatively affected by the difficulty incurred in providing empirical evidence. Literature on this topic is scarce and most of the times the issue of safety is considered jointly with effectiveness. The majority of the articles examined refer to the USA due to its long-standing tradition on OD regulation, which is prone to accept exceptions in the evaluation criteria of trials. For example, the number of patients involved in clinical trials is lower than the number required for common drugs: median value 98 for ODs versus 294 for common drugs [14]. Adverse effects on patients are also considered: in OD trials there is a higher percentage of patients who report serious adverse events (48%), compared to the percentage shown for common drugs (36%) [15]. For European countries, an analysis carried out on the dossiers provided to EMA by pharmaceutical companies during 2000–2010 raised concern on the scarce evidence relating to safety. It was demonstrated that out of 63 ODs approved in that period, in 11 cases, the toxicological studies on two animals – which is a requirement set by EMA – were not carried out [11, 16].

In conclusion, it seems that the evidence on safety produced by OD trials is not optimal. The trade-off between the need to make innovative therapies (often without possible alternatives) soon available to patients with rare disease and the need to produce evidence on drugs' safety has been faced by favouring the former priority. While a common policy has to be found on the safety issue, literature proposals converge on post-marketing controls, which include constrained approvals and/or subsequent revisions [17, 18]. This position implicitly suggests that safety is only partially pursued: While the approval of a drug is based on ex ante safety assessment, an ex post revision of the latter – although appropriate – does not appear to be a definitive solution.

Clinical effectiveness

Clinical effectiveness is an intrinsic requirement to grant the OD status to a product, since – by definition – OD must have

proved to generate a significant benefit. In fact, the European legislation (EC No. 141/2000) [19] lays down that one of the three basics for OD recognition is "... providing a substantial additional benefit to patients' conditions". The problematic issue still lies in clinical evidence, since trials are performed on a limited number of patients. To this extent, two opposite positions are observed in the examined literature, the first one highlighting the possible risks related to a preferential track provided to OD approval and the second one advocating greater flexibility in the process of OD authorization in order to favour patients waiting for a treatment [15–17, 20, 21].

Starting from the first standpoint, an article on USA's experience reports that empirical evidence for OD approval is based on smaller samples (median = 96 versus median = 290 for common drugs) which are less likely to be randomized (30% vs 80%). Orphan and non-orphan pivotal trials also vary in their blinding, with orphan trials less likely to be double-blinded (4% vs 33%) [15].

Similarly, in Europe, Joppi et al. [16] analyse the quality of the OD dossiers submitted to the EMA in the 2000–2010 period and express concern about the small samples ($n < 100$ for one third of trials, $100 < n < 200$ in 50% of cases), the use of randomized clinical trials only for 38 drugs out of 63 approved and the use of placebo as control in 50% of dossiers. Further, the average time for market access is only 20.5 months, within a range of 2–82 months. They also complain about the inadequacy of follow-up periods and the disregard for toxicological analysis.

Looking at the single countries, in the Netherlands, if no alternative treatments are available, less strict effectiveness criteria are applied to OD authorization [11], and in Austria, for the majority of cancer ODs approved, the government applied exceptions to cost-effectiveness criteria, which implies a lower production of long-term empirical evidence [22]. Still within European burdens, Hughes-Wilson et al. [10] condemn "opportunistic" behaviours by pharmaceutical companies aimed at obtaining OD status through proofs of effectiveness based on scarce empirical evidence, as well as short-term follow-up with the risk that, once the OD is marketed, there are no incentives to track the clinical effectiveness in the long run.

With reference to the second strand of literature, authors assume a different position and highlight the difficulties encountered by the producers of ODs in some countries. For example, the Canadian experience does not show a "preferential track" for ODs, and effectiveness criteria should be demonstrated even in the absence of alternative treatments, which can preclude patients' access to care. Janoudi reports a median value of 122 (range 20–247) for OD samples, with a high frequency of studies showing samples' mean between 150 and 299 patients. Specifically, 71% of the studies were based on sample with $n > 150$, and 82.5% of the studies accepted for OD reimbursement were based on at least one randomized double-blind trial [23].

Concern on strict effectiveness requirements is also raised by Dunoyer [17], who examines the policies for OD approval and trading in various industrialized countries, focusing on producers' difficulties to carry out randomized, double-blind, placebo-controlled studies. He suggests a series of "compensatory" measures, such as the implementation of registers tracking information of patients affected by rare diseases (impact of the disease, clinical symptoms, age of onset and rate of disease progression), with data sharing at international level.

The results reported highlight a very fragmented pattern on clinical effectiveness criteria at the international level and suggest the implementation of common rules which on one hand avoid producers' strategic behaviours and on the other hand grant access to treatments by patients with rare diseases. Possible measures are represented by contracts for risk sharing between the manufacturing company and governments, with the aim of tracking long-term information on patients treated. This policy has been implemented, for example, in Australia, where government agreed in keeping the full price of a new OD, based on the demonstration of clinical effectiveness (survival rate) in the long run [24]. Other authors are of the same advice: Denis et al. [25] propose the application of risk sharing measures between the producer and the funding entity (the state), leading either to price reductions if the treatment does not maintain the expected effectiveness or to reimbursement measures conditional upon its cost-effectiveness. Joppi et al. [16] advocate a strict implementation of the rules established by EMA on ODs, thus proposing the introduction of a transitional approval to be definitively confirmed after an observation period.

The effective use of an OD after its approval is another debated issue. In Europe, several products that have been granted OD status (which involves tax and patent benefits) are also effective in the treatment of common diseases. Therefore, once marketed, they benefit from greater distribution and can lead to consistent revenues for the producer.

Costs and economic evaluation

The use of cost-effectiveness criteria in the OD evaluation is widely discussed in the extant literature [10, 16, 20–22, 24–36], which focuses the debate on the main aspects characterizing these drugs: the difficulty in producing empirical evidence, due to the limited data available, [10, 21, 24] and the need to grant equity of access to each patient [5, 8, 10, 11].

The first issue has already been explored in the previous sections: to recall some examples, in Germany, a lower level of significance (compared to common drugs) is required for demonstrating OD clinical effectiveness [37], and in the Netherlands, in the absence of alternative treatments, no pharmacoeconomic evidence is required for a new marketed

OD [11], while in Scotland, a higher cost per QALY (compared to common drugs) is accepted for the OD approval [38].

In the USA, Siddiqui et al. believe that stricter cost-effectiveness measures than those in force for the approval of new cancer drugs should be implemented, as spending on these treatments risks becoming unsustainable and requiring higher premiums from insurance companies [34]. Although contributions are heterogeneous, a common aspect can be found in the examined literature: the need for greater international sharing of the guidelines on cost-effectiveness criteria, not so much for the approval process for ODs but rather for the decisions regarding their reimbursement.

The second issue is more controversial. If we assume that access to care must be ensured to all citizens, cost-effectiveness criteria may be relinquished in favour of equity purposes [11]. When dealing with rare diseases, the choice of funding them implies a benefit for a small percentage of population as against considerable costs for the community [20]. Currently, this issue is particularly debated because the share of public spending devoted to ODs has been increasing in different countries (see next section); as a consequence, eliciting social preferences with respect to ODs has become a policy obligation, well shown by literature. A survey carried out on a sample of Canadian individuals shows that respondents are not willing to pay more for patients with rare diseases compared to "common" patients. Since the parameter adopted to compare the two kinds of treatment is represented by the cost per life's year, the only point supporting ODs is that respondents weigh relevant attributes (e.g., costs, disease severity and clinical effectiveness) similarly for both rare and common diseases. Considering that, on average, rare diseases are more severe, this factor could be decisive in favour of ODs [30]. Another study conducted on 1547 Norwegian citizens shows that – despite the willingness to safeguard equity of access for patients with rare diseases – it is not possible to establish preference for rare diseases, if this goes to the detriment of common drugs [39]. Other sources confirm that, in general terms, society is unwilling to pay for actions that go to the benefit of a very small share of population [7].

The growth of OD consumption in the West requires increasing economic efforts by the National Health Services, already put under pressure by strict budgetary constraints. Internationally shared criteria would reduce any inappropriateness in the OD expenditure, thus reducing the risk of an ineffective use of public resources.

Ethical issues

The debate on access to ODs cannot be separated from ethical considerations, and many references in literature deal with this topic in the countries where healthcare is state's responsibility, the principle of fair access obliges the community to take charge of every citizen's health [30, 32]. In the case of ODs, individual treatment is very expensive and entails the investment of huge sums of money for the benefit of a few. Faced with strict budgetary constraints, however, we wonder whether it is more appropriate – for the same amount of resources invested – to implement programs to the benefit of a few individuals or to extend the benefit to a large share of population, which requires lower individual costs [4, 10]. The OD debate is complicated by the fact that, due to the limited possibility of providing sound clinical evidence, the exemptions granted in terms of clinical effectiveness run the risk of driving the policymakers' financial choices on treatments that may prove ineffective in the long run [4, 8, 10]. Nevertheless, the presence of patients waiting for treatment that can extend their life span or significantly improve their quality of life poses a problem of access to care and obliges policymakers to analyse the equity efficiency trade-off.

Drummond and Towse [7] claim that the concept of vertical equity (different access for different needs) should substitute the better-known concept of horizontal equity (equal access for equal needs). In this perspective, those with greater needs must enjoy greater funding. This step is consistent with the distribution theory to the extent that ODs are actually capable of highly improving the patients' quality of life. In this regard, QALY is indicated by several authors as an appropriate tool to assess the benefits provided by ODs [8, 26, 34].

What several authors criticize, however, is the use of exceptions to HTA principles in the evaluation of ODs compared to common drugs [4, 10]. The question they put is very simple: should the community evaluate differently the clinical benefits experienced by an individual suffering from a rare disease compared to an individual with a common disease, only because in the former case there is a situation of "rarity"? The answer seems to be negative. Other authors share this opinion and, recalling the theory of utilitarianism, underline how ODs and rare diseases are, by their very nature, inconsistent with this theory, as they do not follow the principle of maximizing utility faced with limited resources [32]. The concept of cost-effectiveness in this field cannot be demonstrated, and hence, the bases of utilitarianism are lacking. Largent's contribution in this regard is interesting. He speaks about the between utilitarian criteria and the "rule of rescue" where the latter is dictated by an empathic impulse. The example is that of a diver in grave danger at the bottom of the ocean: with a view to rescuing him - if the operation is possible - the government does not impose budgetary constraints. The exquisitely ethical question is whether this rule should also be applied to rare diseases. The answer can be found in governments' exemption to HTA criteria when dealing with ODs. However, the rising opportunity cost, together with stricter budget constraints, imposes policymakers to find "the appropriate balance between doing a little good for many people and doing a lot of goods for a few" [40].

Another matter for debate regards high unit prices. In many cases, the request to reduce prices, on the basis of HTA criteria, ends up with the failure to market the product, due to its low profitability, with consequent penalization of patients [10]. It is therefore very difficult for policymakers to balance the needs for efficiency with those for equity. Or, according to Pinxten et al., "the challenge results in balancing the principle of equity of access with the constraint on the resources to be allocated to rare diseases" [32]. This issue recalls once again the setting of priorities in the allocation of public funds, which depends largely on collective choices. Literature shows that collective choices tend more to spend public resources for the benefit of many people than of small portions of population [7, 10].

Organizational aspects

The increase in the number of ODs on the market, their high price [10, 11, 27, 29, 30, 33, 34, 41–45] and the implementation of financial incentives have recently led researchers and policymakers to analyse the economic burden that these treatments impose [11, 25], as well as the possible measures to be taken to regulate the sector [10, 11, 21, 25–28, 30, 35, 46].

Although the recent OD trend suggests that these drugs will have a decisive impact on health spending in the years to come, there are still few studies that provide in-depth analyses of the budget impact. Literature's findings do not always agree: In 2004, in Europe, ODs accounted for 0.7–1% of the total resources allocated to drugs, and it was assumed that the said percentage was to rise to 6–8% in 2010 [47]. Those forecasts were later revised downwards. A subsequent study, still referred to Europe, used a simulation model based on the OD unit cost (ranging from a minimum of € 1251 to € 407,631, with a median of € 32,242) and showed that the OD share rose from 3.3% in 2010 to 4.6% in 2016 and then levelled out in the following years [3]. Of the same advice are Hutchins et al., who in 2014 carried out a simulation model for OD spending in Sweden and France: their forecast for 2020 suggested that OD share on pharmaceutical expenditure was expected to increase from 2.7% to 4.1% in Sweden and from 3.2% to 4.9% in France. Although this study mitigates the fear of unsustainable costs escalation due to ODs, some variables, such as the OD approval rate, the expected average sales and the average costs may impact significantly on the predicted values [48]. A more alarmist vision is provided by Denis et al. in a study referred to Belgium, where in 2008 ODs expenditure corresponded to 1.9% of total drug spending and it was expected to increase more than twice (up to 4%) in 2013 [25]. Among European countries, an exception is represented by Latvia, where between 2010 and 2014, the OD market represented 0.84% of the whole pharmaceutical market. State reimburses only 20% of the marketed ODs, and consequently the average OD expenditure is very low compared to other European countries [54,55].

A different scenario is outlined in the USA, where OD consumption does not depend on public reimbursement criteria: recently, over one third of the new approved drugs have been ODs, and the increase – both in relative prices and in the number of ODs in circulation – has raised concern about the cost coverage by insurance companies [4].

It is not clear what the real OD impact on health resources will be, but the growth of this sector and the lack of shared standards for its regulation pose sustainability problems for governments. Some variables will play a critical role in the coming years: (i) the size of the population treated, (ii) the possibility that the treatment may serve for other therapeutic indications and (iii) the limited clinical evidence [8]. Another crucial variable is represented by the reimbursement rate in each country: in Belgium, between 2002 and 2007, the reimbursement of 88% of ODs was approved, compared to 64% for common drugs. In France, over the same period, the percentages were 96% versus 86%, respectively [8].

In Europe, a matter of debate is represented by the financial incentives provided to ODs' producers. The measures implemented in the EU at central level have been initially designed to support small and medium-sized enterprises along a path with uncertain outcomes, especially in case of differentiated reimbursement decisions between the individual member states. The uncertainty, however, seems to be offset by the producer's quasi-monopoly position, which, combined with pressure from patient associations on the funding entity (normally the state), creates a very favourable market niche for the producer and provides the opportunity of setting and maintaining a high price [11, 39]. In 2012, 40 ODs marketed in the EU generated an annual revenue of 200 million US dollars. The average annual individual cost for OD treatment was higher than €150,000 in five European countries (France, Germany, Spain, UK and Italy) with peaks of 1 million euros for specific treatments such as galsulfase. In recent years, these conditions have changed the manufacturers' profiles, thus attracting large pharmaceutical multinationals to the OD market, with the risk of a possible crowding out of small and medium producers on whom the initial incentives had been calibrated.

Considering the high spending for ODs, European governments have recently taken measures to contain their costs: In Italy, the ODs distributed by hospitals are paid 67% of the retail price; in France, tax deductions do not apply if the annual revenue is over 20 million euros [11]. However, these actions, carried out autonomously by each member state, highlight a fragmented pattern and suggest to careful assess the sustainability of a sector that suffers from a regulatory void and may lend itself to strategic behaviours by manufacturers. To contrast this phenomenon, some authors [10] propose that, in the process leading to OD approval, pricing and

reimbursement decisions, a multi-criteria decision model be adopted, in which several variables are carefully considered, namely, (i) disease rarity (the rarer the disease, the higher the research costs, due to the difficulty in providing significant clinical evidence; this variable should be considered when fixing the price), (ii) spreading of research on the disease (the existence of references in literature makes it easier to draft reports and provide evidence for marketing authorization, so companies should be incentivized at producing empirical evidence), (iii) level of uncertainty about clinical effectiveness (the greater the significance of results, the higher the cost to produce consistent clinical results. These circumstances justify a high price and limit the risk of spending public resources on ineffective treatments), (iv) complexity in the molecule production process (the more complex the molecule, the higher the production costs), (v) inclusion of post-marketing follow-up measures (this factor, which entails higher costs, is decisive for verifying the effectiveness of an OD, especially when the previous clinical evidence is scarce), and (vi) disease severity (which is associated with the patients' quality of life, the inability to generate income due to disability and the need for continuous care by family members or caregivers, all variables with an economic burden on society). All these factors provide precious information to the policymakers in the process of evaluating costs and benefits related to the new treatment.

Similar studies implementing multi-criteria analysis in the evaluations of ODs have been carried out in Spain [49] and Belgium [25]. The latter suggests - among the possible measures to reduce the OD pressure on the state coffers - that manufacturers should provide a justification for the price setting, based on a detailed analysis of the investments made and the possible returns from the sale of the product not only within national burdens, but on the international market. The implementation of risk sharing agreements between the producer and the government, based on possible price reductions if the treatment does not maintain the expected effectiveness, or on reimbursement measures conditional upon the effectiveness of the treatment, are also advocated [25].

This brief analysis has highlighted the need for shared standards to regulate the OD sector. The topics most frequently discussed in literature concern the OD budget impact and reimbursability decisions that, due to the exemptions granted in terms of HTA, are not always based on adequate information and hence pose the risk of inefficient public investment.

Discussion and conclusions

This analysis has considered several aspects relating to OD approval, trade and reimbursement.

The contributions investigated regard different countries and include not always homogeneous stances by the various authors, but it is still possible to address useful considerations to analyse a rapidly evolving sector. Over the last decade, the increasing number of ODs in circulation has imposed a growing financial burden on the public health systems, thus raising a number of questions on pricing and exemptions granted to this sector with respect to the implementation of HTA principles.

A recurring theme is high prices. In this respect, there is a need for greater clarity in the investments made by manufacturers and the possible revenue from the OD sale outside the national borders. Moreover, the increasingly significant possibility that, once marketed, ODs may be used to treat more common diseases, requires policymakers to have more control over the intended use of these products.

Much criticism is levelled at the preferential track granted to ODs in the implementation of HTA principles. In this regard, the legislation is not homogeneous, but fragmented and differentiated between western countries. The need for common rules at the international level is underlined, with a view to assessing the sustainability of a sector which, due to this regulatory void, can lend itself to producers' strategic and opportunistic behaviours.

The exemptions granted on proving effectiveness for the purposes of facilitating quick access to ODs by patients waiting for treatment entail the risk of a significant investment of public resources for treatments that may prove ineffective in the long run. With specific reference to this point, the budget impact analysis is considered a useful tool to identify investment costs and results in the long term and to assess the opportunity cost of the choice to encourage the OD production. Within this analysis, it is desirable to use multi-criteria choice models that consider a number of variables that are useful to evaluate both pricing and OD reimbursability criteria.

Finally, the measures requiring fast implementation include the creation of internationally accessible registers containing all the follow-up information regarding the safety and clinical benefit of each OD [51]. This information, which can be stimulated through the direct involvement of patients' associations and their families [50, 52, 53], is of utmost importance to ensure the minimum level of effectiveness that cannot be currently guaranteed due to the exemptions granted on the HTA criteria. The uncertainty characterizing this sector poses severe sustainability issues regarding the possibility of continuing to invest in ODs and pushes policymakers to set healthcare investment priorities that are as close as possible to collective preferences.

Authors' contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Elenka Brenna, Barbara Polistena and Federico Spandonaro. The first draft of the manuscript was written by Elenka Brenna, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Ethics approval No plagiarism and no conflict of interest can be addressed to this research. The paper is authored jointly by Elenka Brenna, Barbara Polistena and Federico Spandonaro.

Appendix

Table 1 Main findings from literature review addressing each of the selected domains – exemplar studies

	Country	Main findings	Parameters	Authors
Safety	USA	N° of patients for clinical trials lower than the threshold	Median value 98 for ODs* versus 244 for CDs**	Downing et al. (2014) [14]
	USA	Higher percentage of patients reporting adverse events	48% for ODs versus 36% for CDs	Kesselheim et al. (2011) [15]
	Europe	Scarce production of evidence for safety issues	Out of 63 ODs approved, in 11 cases, the requirement of toxicological studies on two animals was not performed	Joppi et al. (2013) [16]
Clinical effectiveness	USA	i. Samples less likely to be randomized ii. Orphan trials less likely to be double-blinded	i. 30% for ODs versus 80% for CDs ii. 4% for ODs versus 33% for CDs	Kesselheim et al. (2011) [15]
	Netherlands	Effectiveness criteria are less strict in the absence of alternative treatments	Clinical effectiveness criteria	Michel and Toumi (2012) [11]
	Canada	In Canada, no preferential tracks for effectiveness criteria	71% of studies was based on sample with $n > 150$ and 82.5% of studies accepted for OD reimbursement was based on at least one randomized double-blind trial	Janoudi et al. (2016) [23]
	Europe	For 63 OD approved in 2000–2010 i. Small samples ii. Scarce use of randomized clinical trials iii. Low average time for market access	i. $N < 100$ for one third of trials, $100 < n < 200$ in 50% of cases ii. Clinical trials applied only for 38 approved ODs out of 63 iii. 20.5 months, within a range of 2–82 months	Joppi et al. (2013) [16]
Costs and economic criteria	Scotland	Higher threshold for cost per QALY (compared to common drugs) is accepted for the ODs' approval	Cost per QALY	Kawalec et al (2016) [38]
	Canada	No social preference for the ODs' public funding compared to other drugs.	Willingness to pay per life's year	Mentzakis et al. (2011) [30]
	Norway	It is not possible to establish preference for rare diseases, if this goes to the detriment of common drugs	Choice between funding treatment for a rare disease versus a common disease, in presence of budget constraint. Revealing attitude to equity on a five-point Likert scale	Desser et al. (2010) [39]
	USA	Stricter cost-effectiveness measures for OD are advocated, due to unsustainable costs	Cost-effectiveness criteria	Siddiqui et al. (2012) [34]
Organizational aspects	Europe	Concerns on the impact of ODs on pharmaceutical spending	The OD share over the total pharmaceutical expenditure rose from 3.3% in 2010 to 4.6% in 2016, and then levelled out in the following years	Schey et al. (2011) [3]
	Belgium, France	Reimbursability issues	In Belgium, between 2002 and 2007, the reimbursement of 88% of ODs was approved, compared to 64% for common drugs. In France, over the same period, the percentages were 96% versus 86%, respectively	Iskrov et al. (2014) [8]
	France, Germany, Spain, UK and Italy	i. Financial incentives provided for ODs' production ii. High per capita costs	i. Between 2002 and 2009 EU provided funds with an annual average of approximately 40 million euro for scientific research on rare diseases ii. The average annual individual cost for OD treatment was higher than €150,000 in five European countries (France, Germany, Spain, UK and Italy) with peaks of 1 million euros for specific treatments.	Michel and Toumi (2012) [11]
Ethical aspects	USA	Disapproval to the use of exceptions to HTA principles in the evaluation of ODs	Should the community evaluate differently the clinical benefits experienced by an individual suffering from a rare disease compared to an individual with a common disease, only because in the former case there is a situation of "rarity"?	Danzon (2018) [4]
	–	Collective choices tend more to spend public resources for the benefit of many people than of small portions of population	Trade-off equity efficiency	Drummond et al. (2014) [7]

*OD orphan drug

**CD common drug

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