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What Is Wrong with Orphan Drug Policies? Suggestions for Ways Forward

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ABSTRACT

We argue that orphan drug policies have been useful in incentivizing socially desirable R&D and that in their absence it is unlikely that treatments of any kind would have emerged. Weaknesses in the current policy framework need to be addressed by refining this framework rather than altogether replacing or dismissing it as inefficient. Improvements can be made in data collection, and efforts are already under way at the European Union level with initiatives concerning registries. Similarly, the legislative framework can be refined to define when an orphan treatment is "sufficiently profitable," at what stage should profits be considered excessive, and, consequently, whether any favorable conditions offered to manufacturers should be removed. Concerns about availability and accessibility of orphan drugs, which are valid in many instances, do not imply that the current orphan drug policy framework is deficient but that the means of assessment need to be improved upon for realistic and affordable prices for payers to become the norm. This implies better data quality, the possible extension of the criteria for value assessment to take explicitly into account the peculiarities of rare diseases, and the availability of appropriate benchmarks around rare disease cost and quality of life to conduct meaningful value assessments.

Keywords: access to health care, orphan drugs, pricing and value assessment, rare diseases, regulatory.

In a recent study by Cote and Keating [1], the authors discussed the effects of orphan drug policies on availability, accessibility, and fairness and adopted a qualitative and inductive approach using grounded theory [2]. In this article, we discuss some of their article's salient features and offer our perspective on orphan drug policies.

In their critique of orphan drug policies, Cote and Keating raise four issues; these merit further commentary. The first relates to the argument that orphan drug policies provide an incentive for manufacturers to concentrate on lucrative areas such as oncology, as evidenced by the higher proportion of oncology treatments developed compared with other therapy areas. While the outcome in terms of drugs produced cannot be disputed, the likely link between orphan drug policy *intent* and its actual *outcome* should be interpreted with caution, in the absence of several parameters in the analysis that may influence this outcome; for example, a key reason why more cancer therapies may have been discovered and marketed could be that many potentially treatable rare diseases—about 22% of them—are (rare) cancers [3], although this figure still needs further clarification [4]. The higher proportion of rare cancers could also be a result of an increased incidence of cancer, which is a consequence of an ageing population [5–7]. It may also be a consequence of government funding programs targeting cancer treatments (e.g., New Drug Funding Programme implemented by Cancer Care Ontario in Canada) or other regulatory measures implemented to address gaps in value assessment (e.g., supplementary advice for end-of-life treatments issued by the National Institute for Health and Clinical Excellence in England) [5]. Overall, the argument about the likely lucrative nature of cancer treatments could provide part of but not all the explanation.

The second issue is the problem of accessibility due to high prices. While we agree in part with their assessment, the authors provide no arguments to advance the debate on returns to innovators and on access. Orphan drug prices are constantly questioned and contested in the literature, the main issue being whether or not they deserve "special status" because of the small number of patients affected and whether rarity can provide the justification for a higher price. Some argue that all patients should benefit from the same quality of care based on equity and on societal preferences [8,9]; others believe that it is a question of opportunity costs or costs forgone from treating one patient with a rare condition versus a much larger number of patients with a "normal" condition with similar characteristics [10]. Our view is that the above arguments present problems in their conceptualization because of three conflicting elements: first, there is complete absence of appropriate benchmarks and metrics to gauge whether prices are low, high, or too high relative to expectations; prices are relative to value and a pertinent question in this context is whether all value parameters have

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been (or can be) incorporated in informing pricing decisions. Second, it is socially desirable to develop treatments for conditions carrying very high disease severity or having significant unmet medical need—irrespective of their rarity—and for appropriate returns to be awarded to innovators; and third, in the context of orphan drugs, this desire is supported by a regulatory framework, which, in principle, should make the cost of drug discovery and development lower, as also acknowledged by the authors.

In assessing value and, consequently, rewards to innovators, our standard tools are not necessarily sufficient to take these considerations into account; lack of data and incomplete registries are partly responsible for this. Efforts are currently being made to address this—at least in part—and create the evidence base about the cost of a number of rare diseases and the quality of life of patients with rare disease and their carers through the Burden of Disease and Quality of Life project [11]; further efforts are undertaken to leverage as well as coordinate registries; indeed, there are four complementary European Union initiatives to improve patient registries for rare diseases: the EPIRARE project, the PARENT joint action, the EUCERD joint action, and the International Rare Disease Research Consortium. The overall aim of these initiatives is to establish common data sets, quality criteria, and a political framework [12]. The creation of this evidence base and the above networks and initiatives is long overdue and could act as a benchmark or proxy benchmark in value assessments of new orphan treatments.

The third issue identified is the lucrative business opportunities for manufacturers in developing orphan drugs in general. It is undeniable that there have been cases in which certain orphan drugs have had very high returns. Again, to argue whether these have been excessive or not, appropriate benchmarks are needed. Such benchmarks would be useful to assess whether high or excessive returns are a problem specifically for orphan drugs, or whether this is general to targeted therapies characterized, for example, as treatments for severe or life-threatening conditions, curative therapies, or where no other treatment alternatives exist.

The fourth issue relates to the explanatory factors for the excessive focus on orphan drugs and their profitability for manufacturers that have been put forward by the authors, although it is not clear in which manner they were identified. Among them are fast-tracking and protocol assistance, excessive stratification of diseases, old molecules being rediscovered for orphan indications, and off-label use of orphan drugs. Fast-tracking and protocol assistance is not unique to rare diseases and orphan drugs, although these are indeed more likely to be eligible. The former relates to the overall regulatory framework for pharmaceuticals, stating the conditions under which patients may benefit from early access to treatment [13–15]. Protocol assistance was explicitly implemented to encourage orphan drug development and access, since given the small number of patients affected, it is more challenging to generate robust evidence [16]. Our view is that protocol assistance is necessary across the board to ensure that all stakeholders concerned (regulators, manufacturers, and patients) are involved in the generation of appropriate evidence that, ultimately, benefits society.

The issue of excessive stratification of diseases and multiple indications of orphan drugs (salami slicing) has been debated widely in the literature [9,17,18]. It is undeniable that disease targets have in many instances become narrower and the scientific ability to address narrow disease targets has over time become greater. Our view is that we ought to see this as an achievement rather than as a handicap or a nuisance. Ultimately, any argument about the stratification of diseases and whether these are justifiable or not need to be addressed by scientific evidence; if peer reviewed scientific validation is provided to justify a new indication, then the policy question is how to assess value in this indication. This raises—again—the issue of price relative to value and the comparison of proposed prices against objective benchmarks about the cost to sufferers, carers, and society. Further, evidence shows that prices tend to be set according to a product's single indication and do not consider its total prevalence across the multiple indications[19]. This may indeed generate excessive returns to manufacturers and may need to be addressed more aggressively by regulators. In such cases, for example, Article 8.2 of the European regulation on orphan drugs may apply, where the 10-year market exclusivity period could be reduced if the product is shown to be sufficiently profitable [20].

It is true that old molecules are often rediscovered for a new indication—in some cases orphan—and that the pricing arrangements for a new use are unsatisfactory. High prices of orphan drugs have been explained as mainly a consequence of a monopolistic position, and consequently on the willingness to pay for the treatment [9]. We may ask ourselves, however, whether this price setting that is based on willingness to pay is any different from what we see in other disease areas? Here the key issue is that the evidence accepted for orphan drugs tends to be less robust than for other drugs and the question remains whether this should be acceptable over the longer term.

Finally, the argument is put forward that the off-label use of orphan drugs provides another business opportunity. As much as this statement can be true, we would argue that this is an issue that is not specific to orphan drugs but to most other therapy areas and, particularly, cancer (including pediatric cancer) treatments [21].

In conclusion, orphan drug policies have been useful in incentivizing socially desirable R&D in a sensitive area of public policy. In the absence of the present framework, it is unlikely that treatments of any kind would have emerged. Where weaknesses can be identified, these need to be addressed in the context of the existing framework rather than altogether replacing it or dismissing it as inefficient. For example, improvements can be made in data collection, and efforts are already under way at the European Union level with initiatives concerning registries.

Similarly, the legislative framework can be refined to define when an orphan treatment is "sufficiently profitable" and at what stage should profits be considered excessive and, consequently, whether any favorable conditions offered to manufacturers should be removed. Concerns about availability and accessibility, which are valid in many instances, do not imply that orphan drug policy frameworks are deficient but that the means of assessment need to be improved upon for realistic and affordable prices to become the norm. This implies better data quality, the possible extension of the criteria for value assessment to take explicitly into account the peculiarities of rare diseases (e.g., severity, paucity of evidence), and the availability of appropriate benchmarks around cost and quality of life of rare diseases to conduct meaningful value assessments.

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