ADDING UNCERTAINTY TO INCENTIVISE INVESTMENTS IN RISKY AREAS

An economic perspective on how the European Commission's proposal to direct incentives towards areas of high unmet medical need could nullify them

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Despite the significant progress made in the treatment of rare diseases in the past two decades, 95% of rare diseases still lack an approved treatment.[1] The lack of authorised treatments mostly concerns the rarest of rare diseases: 79% of rare disease patients suffer from 149 of the most prevalent rare diseases, with a prevalence between 1 and 5 in 10,000.[2]

Many of these diseases have an authorised treatment.[3] This suggests that more investments in medicine development in the rare disease space today are directed towards the most prevalent of the rare diseases where at least one existing treatment often exists.

On the surface, this could be puzzling: Why would companies keep innovating in a crowded market where people living with rare diseases already have an authorised treatment (red ocean), instead of entering disease areas where no competing treatment exists (blue ocean)? There are good reasons for this. First, despite the availability of authorised treatments, unmet medical needs still exist. Second, and the primary focus of this article, investing in uncharted territory where no authorised treatment exists is riskier compared to investing in a disease where one or more treatments have already been developed and successfully launched.[4]

The risk difference is significant enough that the promise of a blue ocean from the perspective of an investor does not fully counterbalance it.

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1 European Commission (2020). COMMISSION STAFF WORKING DOCUMENT EVALUATION. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products {SEC(2020) 291 final} - {SWD(2020) 164 final}. Brussels, 11.8.2020, SWD(2020) 163 final. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020SC0163. Note that this does not correspond to 95% of rare disease patients lacking an authorised treatment because many authorised treatments are indicated for the most prevalent of rare diseases, affecting a larger share of rare disease patients.

2 79% (mid-point between 77.3% and 80.7%) of rare disease patients suffer from 149 of the most prevalent diseases, with prevalence between 1 and 5 in 10,000. See Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., Murphy, D., Le Cam, Y., & Rath, A. (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics: EJHG, 28(2), 165–173.

3 Of the 142 EMA-approved OMPs by 2017, 61 (43%) are indicated for a rare disease with a prevalence between 1 and 5 in 10,000. See European Commission (2000). The number of rare diseases covered might be lower since more than one OMP could be approved for the same indication.

4 Developing a medicine and bringing it to the market are risky endeavours. This is well recognised in the literature, with estimates suggesting that only one in ten compounds that enter Phase I clinical trials succeed in obtaining regulatory approval. In the rare disease space, medicine developers face specific risks and hurdles due to, for instance, the small and dispersed patient population and the limited knowledge about the disease. See, for instance, Sun, D., Gao, W., Hu, H., & Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it? Acta pharmaceutica Sinica. B, 12(7), 3049–3062.

The European Commission wants investors to focus on the blue ocean

One of the objectives set by the European Commission for the revision of the EU pharmaceutical package is to incentivise investments in blue ocean areas where little research is undertaken and no treatment is currently available, areas of High Unmet Medical Need.[5]

On 26 April 2023, the European Commission published its proposal. The tool the European Commission chose to incentivise investments in these areas of High Unmet Medical Need is one additional year of protection, the Orphan Market Exclusivity. Companies can obtain this additional year of Orphan Market Exclusivity if they can prove that (i) there is no authorised medicine for the condition or the new product brings exceptional therapeutic advancement and (ii) the new product results in a meaningful reduction in disease morbidity or mortality.[6]

In other words, the European Commission seeks to compensate investors for the larger risk of entering uncharted blue ocean territory by adding one year of Orphan Market Exclusivity. The European Commission believes investors will then start investing more in diseases with no authorised treatment, often the rarest of rare diseases.

Investors can gain access to the additional year of Orphan Market Exclusivity if their medicine is classified as serving a High Unmet Medical Need. However, based on the current understanding, this seems a risky endeavour. Interviews with stakeholders in the rare diseases space suggest that the definition of High Unmet Medical Need is uncertain, with no opportunity to re-submit using new data or appeal a negative decision taken at the time of regulatory approval.

Thus, the European Commission proposes to compensate investors for the additional risk of entering uncharted territory through a mechanism that adds risk.

It is likely that investors would base their investment decisions on the (now lower) baseline level of years of Orphan Market Exclusivity. If not properly managed, the risk associated with the additional year of Orphan Market Exclusivity could jeopardise the intended benefit of the additional year.

To follow the good intentions of the European Commission, a modulated system of incentives should use an objective mechanism. The European Expert Group on Orphan Drug Incentives has proposed such a mechanism where the classification that allows for longer Orphan Market Exclusivity is based on the number of existing authorised medicines for the indication.[7]

On a final note, we should not expect tweaking incentives at the margin (e.g., adding one year of protection) to be sufficient to overcome all the barriers to bringing new medicines to rare disease patients where none exists. Risks and barriers cumulate along the development path, rendering a single protection tool ineffective. Different, more targeted tools are needed, which in many cases could be based on partnerships.[8]

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5 European Commission (2021). A pharmaceutical strategy for Europe. Available https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN.

6 European Commission, Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, Article 70.

7 See European Expert Group on OD Incentives "Modulating Incentives for OMP Development: Modulation framework and policy proposals", available at https://drive.google.com/file/d/1hf8FOrOpJWDPPFiNjNpPQ5RhHU3qUaMW/view.

8 See Copenhagen Economics (2021). Innovating for people living with a rare disease. Available at https://copenhageneconomics.com/wp-content/uploads/2023/03/Innovating-for-people-living-with-a-rare-disease_Copenhagen-Economics_1703_2023.pdf.