Copenhagen Economics

ENABLING, NOT REWARDING

How to design a high unmet medical needs category to drive, not deter, innovation in orphan medicinal products

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Changing the paradigm

In April 2023, the European Commission proposed a change in the incentive system for developing orphan medicinal products[1] (OMPs) with the ambition to direct research and innovation into two areas i) radical innovation to produce transformative OMPs that offer an exceptional therapeutic advancement and ii) rare diseases with no authorised treatment.[2] What the European Commission collectively refers to as areas of High Unmet Medical Need (HUMN).

While the two-fold ambitions must be shared by everyone, the means must not. Evaluating Orphanet data, this note illustrates the preconditions for innovation in rare disease treatments as a basis for an informed further development of an EU incentives system.

The European Commission's proposal represents a regime shift in the way we incentivise OMP development. From today's system where incentives, such as 10 years of Market Exclusivity, make the investment case for innovation in OMPs possible to a reward-based system offering a prize for successfully bringing a HUMN treatment to the market and reducing the incentives elsewhere. The European Commission suggests nine years of Market Exclusivity to non-HUMN classified medicines, a reduction of one year from the current 10 years. For HUMN classified medicines it suggests bringing back the lost year getting to the current 10 years. See Table 1.

Table 1
Changes to Market Exclusivity

OME	Status quo*	EC proposal**	EP position***
Baseline	10 years	9 years	9 years
HUMN	-	10 years	11 years

Source: (*) Regulation (EC) No 141/2000; (**) European Commission proposal for a Regulation published on 26 April 2023 [see link]; (***) European Parliament position adopted in plenary vote on 10 April 2024 [see link].

While a reward-based system that focuses on the end goal may sound enticing, it ignores the nature of OMP development and fails to address the core challenges of bringing HUMN OMPs to people in need.

[1] Orphan medicinal products are intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union.

[2] The European Commission proposal for a Regulation is available here.

The lack of OMPs addressing HUMN is not due to the lack of a prize. Instead, we find that it is primarily caused by an insufficient body of knowledge available about disease mechanisms. The build-up of that knowledge is stepwise and often requires many treatments that serve as enablers. Thus, it cannot be solved by a narrowly defined prize. Instead, the regime shift may depress innovation to the detriment of patients in Europe and globally. However, if the HUMN reward is defined broadly enough it may still incentivise the continuous build-up of knowledge.

On 10 April 2024, the European Parliament adopted its position on the Commission's proposal. The Parliament compromise maintains the baseline Market Exclusivity protection at nine years but elevates it to 11 years for HUMN-classified medicines. See Table 1. It also broadens the definition of HUMN by clarifying that the benefit should be assessed taking into account the relevant patient population. This broadening of the definition is an improvement over the European Commission's proposal as it ought to make the HUMN classification applicable to more development projects thereby serving more as an enabler than a narrowly defined reward.

Adding one year, compared to the current 10 years will also increase innovation as one more year reduces the commercial risk for companies of initiating a development project for a first-in-condition treatment. The reason is that one more year of Market Exclusivity mitigates the uncertainty around the market potential of the medicine (such as number of patients and the expected price that payers are willing to pay) as no previous medicine has paved the way for that information.

The European Parliament compromise is a step in the right direction. However, the question remains how restrictive the definition of HUMN should be to act as an innovation-enabling incentive rather than a reward.

Transformative orphan medicinal products require knowledge

Transformative OMPs that offer an exceptional therapeutic advancement are often the result of incremental progress rather than isolated 'jumps'. Each OMP that is made available to patients contributes to building up the necessary body of knowledge, eventually making it possible to develop and market a transformative treatment while adding patient value along the way.

Consider the treatment for cystic fibrosis approved by the European Medicine Agency (EMA) in 2020, almost 30 years since the mutation in the gene called CFTR causing cystic fibrosis was identified. This therapy came as the *ninth* treatment option, and has received a "major benefit" assessment rating from the German Federal Joint Committee. Based on this it could potentially be seen as 'transformative'.

As this treatment reached the market stage, cystic fibrosis was one of the most researched rare diseases according to the number of research projects related to it.[3] Its predecessors not only advanced the knowledge base but also brought value to patients. Six predecessors provided clinically relevant advantages.[4] Furthermore, they brought treatment options to a broader patient base; starting from 6% of patients back in 2012 when the first modulator reached the market to an estimate of 90% of cystic fibrosis patients today.[5]

There are still patient groups that do not respond to the current CFTR modulator treatments. In addition, patients on CFTR medicines still experience long-term lung function decline. There is therefore a need for treatments with alternative mechanisms of action to address remaining unmet medical needs.

If the Commission's proposal had been in force back then, perhaps only *the first* and *the ninth* treatment would qualify for the HUMN category and have benefitted from the 10 years of OME even though it may have been the seven in-between-treatments that gradually added to the knowledge base of cystic fibrosis, thus allowing for the ninth treatment to be developed.

[3] See Figure 12 in Letinturier-Valencia MC, Chan C-H, Rath, A., Julkowska D, Eds (2022). IRDiRC State of Play: Rare Diseases Research Initiatives 2019-2021.

[4] Six out of eight prior treatments are OMPs. Goetz, D. M., & Savant, A. P. (2021). Review of CFTR modulators 2020. *Pediatric pulmonology*, 56(12), 3595-3606 outlines the positive effects of CFTR modulators.

[5] McGarry, M. E., & McColley, S. A. (2021). Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatric pulmonology*, 56(6), 1496-1503.

Reducing the incentives for their development as proposed by the European Commission could have slowed down or even halted innovation, thus never allowing the 'transformative' treatment to be developed. In order words, it is key to keep incentives sufficiently high to sustain ongoing innovation which eventually may lead to transformative treatments.

Table 2
The ranks of the six treatments with a "major benefit" rating and related rare disease area

Rank of "major benefit" treatment	Rare disease
1st	Spinal muscular atrophy (SMA)
1st	Metachromatic leukodystrophy
3rd	Renal cell carcinoma*
4th	Gastrointestinal stromal tumour*
9th	Cystic fibrosis
10th	Multiple myeloma*

Note: *Rank* refers to the position of a treatment option at the time when treatment with a "major benefit" rating was brought to the market. (*) indicates a rare cancer.
Source: Copenhagen Economics based on information published on the German Federal Joint Committee website.

The treatment mentioned above for cystic fibrosis is one among six treatments that were granted a "major benefit" rating from the German Federal Joint Committee (G-BA). This is the highest benefit rating by the German Health Technology Assessment body. "Major benefit" corresponds to a sustained and large improvement in therapy benefits that were not previously achieved by the appropriate comparator. This could include recovery from disease, a considerable increase in life, long-term relief from severe symptoms or extensive avoidance of severe side effects.[6]

Among these six treatments, four, including the treatment of cystic fibrosis, were brought to the market as the second or later treatment option for a disease. See Table 2. The other three, not surprisingly, are rare cancer treatments where drug development benefits from an established research ecosystem and significant patient engagement.[7] Again, we see the link between accumulated knowledge and the likelihood of developing transformative treatments.

The remaining two treatments that were transformative *and* first in condition were notably gene therapies. The historical build-up of knowledge allowed the development of this technology which has great potential for the treatment of many rare diseases.

At this point, we do not know how restrictive the HUMN definition will be and how the European Commission would apply the exceptional therapeutic advancement condition in practice.

Our analysis shows, that if the application would result in outcomes mirroring the G-BA definition of a major benefit it will be too restrictive as it would reward only very few treatments.[8] Instead, we analyse 381 European Public Assessment Reports (EPAR) published by the EMA to tease out a better way of applying such a definition. See the grey box on the next page for how we have developed results.

At one extreme, we find that only 6% of treatments would have qualified for HUMN under a strict definition[9], see the leftmost column in Figure 1. At the other end, 62% of treatments would have qualified under a wider definition, see the rightmost column in Figure 1.

The wider definition would support the innovation process as we have advocated for. But since 52% treatments already qualified for orphan designation, which is not so far from 62%, the current orphan designation seems to be a good and workable solution. And this is the current system linking years of Market Exclusivity to the orphan designation.

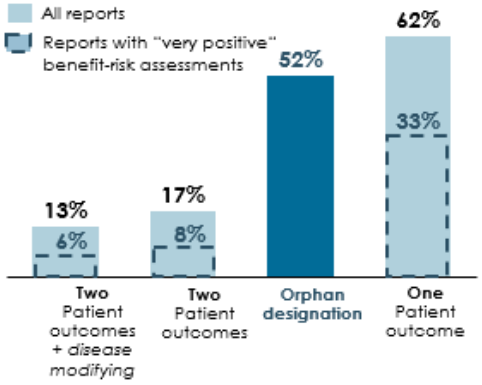
[6] See section 3.2 in OECD (2018). Pharmaceutical reimbursement and pricing in Germany.

[7] See e.g. Sharifnia, T., Hong, A. L., Painter, C. A., & Boehm, J. S. (2017). Emerging opportunities for target discovery in rare cancers. *Cell chemical biology*, 24(9), 1075-1091.

[8] Since 2011, only 3% of rare disease treatments scrutinized by GB-A (six out of 197) have received the highest "major benefit" rating. This share increases to 14% if we also add to the analysis treatments with the second highest "considerable benefit" rating.

[9] Our strict definition implies that the treatment must show evidence of slowing down the disease progression, must improve at least two out of three patient outcomes (symptom relief, increased mobility, or survival) and must have a very positive benefit-risk assessment.

Figure 1
Share of EPAR reports indicating specific clinical benefits



Note: Based on the analysis of 381 EPAR reports applying methodology as outlined in the grey box.
Source: Copenhagen Economics.

Methodology

We characterise transformative treatments as those that fulfil the following three criteria.

1. They must show evidence of slowing down disease progression (disease-modifying).
2. They must improve two out of the following three patient outcomes: symptom relief (feel), increased mobility (function), or survival.
3. They should have a "very positive" risk-benefit assessment i.e., the clinical benefits should outweigh the potential side effects.

In our analysis, we rely on information from 381 European Public Assessment Reports (EPAR), published by the European Medicine Agency (EMA) since 2007, which cover medicinal products with rare disease indications. These treatments are identified using the Orphanet Orphan Drug database.

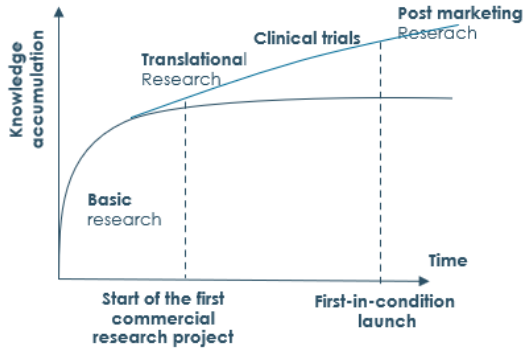
We then use ChatGPT to extract information on criteria (1) and (2) from the EPAR reports. Additionally, we conduct sentiment analysis of *Benefit-Risk assessment* chapters to serve as a proxy for criterium (3). We rate the sentiment on a scale from -5 to 5, where -5 is extremely negative, 0 is neutral, and 5 is extremely positive. We consider *Benefit-Risk* chapters with sentiment scores between 3 and 5 as having a "very positive" assessment. We program EPAR collection and analysis in Python.

First-in-condition

If a robust knowledge base is indispensable for driving OMP development forward toward a truly transformative treatment, it is no less true for developing the first authorised treatment for a rare disease.

Prior research shows that the discovery and development of medicines build on fundamental (basic) research[10,11] and that it takes time before the body of research accumulates to a point where a commercial research project can be justified in a pharmaceutical company.[12] This we have illustrated in Figure 2 which shows how a sufficient level of basic research is needed before a commercial project can be initiated.

Figure 2
Role of knowledge accumulation in the first in-condition medicines development



Source: Copenhagen Economics.

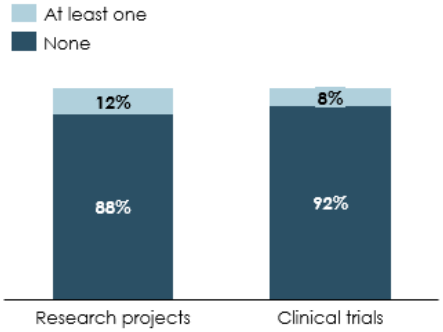
[10] Spector, J. M., Harrison, R. S., & Fishman, M. C. (2018). Fundamental science behind today's important medicines. Science Translational Medicine, 10(438).

[11] Liu, X., Thomas, C. E., & Felder, C. C. (2019). The impact of external innovation on new drug approvals: A retrospective analysis. International Journal of Pharmaceutics, 563, 273-281.

[12] Cleary, E., Jackson, M. J., & Ledley, F. (2020). Government as the first investor in biopharmaceutical innovation: Evidence from new drug approvals 2010–2019. Institute for New Economic Thinking Working Paper Series, (133).

Most rare diseases that lack authorised treatment in the European Union today also lack adequate research, hindering the development of pioneering treatments. As shown in Figure 3, as much as 88% of the rare diseases that lack an authorised treatment also lack research, with 92% having no recent history of clinical trial activity. Rewarding the scientific effort of bringing a first-in-condition treatment is important and should remain a cornerstone of a future EU incentives system. However, this alone will not incentivise their development as it does not address the key underlying barriers of knowledge scarcity.

Figure 3
Most of the rare diseases without authorised treatment in the EU lack research



Note: The sample of 6604 rare diseases without an authorised treatment. Research projects are defined as "ongoing and unpublished research projects funded by a funding body with a scientific committee performing a competitive selection or issued from the regular national research funding". The trials can be ongoing, recruiting, or finished.
Source: Copenhagen Economics based on Orphanet.

Against this background, a narrowly defined HUMN classification can actually become a barrier to innovation contrary to the stated ambitions of the European Commission and European Parliament. Once the first OMP for a disease has been authorised to receive the HUMN reward, the likelihood that the next OMP will be transformative thereby also receiving the HUMN reward is low. With corresponding fewer years of Market Exclusivity (nine years instead of 10 years) and still a limited body of knowledge, there is a real risk that the innovation process for that particular disease will stifle.

Finally, in addition to the lack of knowledge base, first-in-condition also carries higher business-related risks when compared to the treatments that follow. These include the difficulty in predicting the actual number of patients, how the patient will react to the treatment and whether the payers will be willing to pay for the treatment.[13] This added business risk needs to be mitigated by additional years of market exclusivity. This is why the European Parliament proposal, by adding one year of Market Exclusivity getting to 11 years, is an improvement over the current 10 years which is what the European Commission proposes to keep.

Enabling innovation must therefore remain the guiding principle

In conclusion, while the idea of a reward-based system may seem appealing, defined narrowly it will undermine the innovation process that needs a sufficient knowledge base to both find the first-in-condition and later find the transformative treatment. This fact is largely ignored in the European Commission Impact Assessment and puts into question a predicted 10% increase in OMPs addressing HUMN that would result from shifting to a reward-based system.[14]

Instead, incentives should, as they are today, focus on supporting the *process* of innovation. The definition for high unmet medical needs, therefore, should not be too restrictive as it will not act as an incentive but a reward. It is important that all relevant stakeholders, including patient representatives, take part in defining the high unmet medical needs category and provide guidance on its implementation. Furthermore, incentives should be strengthened in areas with limited knowledge about a particular disease to foster innovation in orphan medicinal products.[15]

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[13] European Expert Group on Orphan Drug Incentives. (2023). An EU HTA fit for rare diseases.

[14] See p. 51 in Commission Staff Working Document, SWD(2023) 192 final [see link].

[15] European Expert Group on Orphan Drug Incentives. (2022). Modulating Incentives for OMP Development: Modulation framework and policy proposals" [see link].