Rare diseases

SME BioForum report 2023

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Background

A rare disease affects fewer than 5 in 10,000 persons. It is estimated that there are 6000 to 8000 life-threatening or chronically debilitating rare diseases affecting more than 36 million people in Europe. Collectively, rare diseases are not rare.

Many rare diseases manifest themselves in childhood, resulting in a shortened lifespan and a dependency on care throughout the patients' lives. Due to the low prevalence of each disease, medical expertise is rare, care offerings inadequate, and research limited. Taking several years to be diagnosed and with a lack of effective treatments, rare diseases cause significant suffering to the patients and their families and result in high costs for individuals and society.

In January 2000, the European Commission introduced the EU Orphan Regulation. This regulation was meant to incentivise the research, development, and placement on the market of products intended to diagnose, prevent or treat rare diseases (i.e. orphan medicinal products). Medicinal products eligible for these incentives are identified through the EU orphan designation procedure. The orphan legislation in the EU has allowed for over 2,734 orphan designations issued by the European Commission, of which 231 have already resulted in authorised medicinal products.

On February 28th, 2023, Rare Disease Day, EuropaBio's Small and Medium-sized Enterprises (SME) Platform organised a session on rare diseases and invited European SMEs to share their experiences and discuss the current regulatory and incentives framework ahead of the revision of the pharmaceutical legislation and the legislations on orphan and paediatric medicines. Participants discussed Research and Development, Regulation, and the European Market and investment environment.

36 million

people in Europe are affected by a rare disease

There are more than

6000

RARE DISEASES

MANY RARE DISEASES

manifest themselves in childhood,

Science, Research and Development

Each rare disease affects a small number of people, which brings significant challenges in clinical trial design and recruitment, alongside the limited knowledge of the overall clinical evidence and disease progression process over time (i.e. disease "natural history").

To overcome these challenges, the benefits of data sharing are multiple, including reducing duplication of efforts and costs, enabling engagement with experts and the patient community and supporting clinical trials.

Patient registries are important data sources on healthcare practices, medicines' uses and clinical outcomes. They may provide information on epidemiology, standards of care and treatment patterns for rare diseases. However, the prohibitively high costs of these registries make them inaccessible for smaller companies.

Developing orphan medicinal products may raise complex scientific issues. The orphan legislation makes it possible to request protocol assistance from European Medicines Agency (EMA) in addition to scientific advice. However vital and valued, SMEs still consider that scientific advice could be faster and more tailored to their needs.

Despite these challenges, SMEs still drive rare disease research and innovation. In 2020, SMEs developed almost 20% of all human medicines recommended for authorisation in the EU, half of which targeted a rare disease.

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Recommendations

- **Increase funding towards basic research -** to improve disease knowledge, uptake new technologies and tools (such as artificial intelligence), support pre-clinical screening of new drugs, and validate drug candidates.

- **Adopt flexible clinical trial endpoints for rare diseases -** accept natural history data for endpoint development and encourage new tools for endpoint design.

- **Regulatory flexibility for clinical trial design -** allowing for natural history data if it is available, not using placebo groups and consenting synthetic control arms.

- **Incentivise patient registries' access and use for smaller companies -** with engagement between registries, industry and regulators to define specific outcome data to be collected and develop new outcome measures for pivotal studies (i.e. to confirm the safety and efficacy of treatment).

- **Provide faster and more tailored scientific advice for smaller developers -** build on the EMA's work, including its current PRIME scheme to further assist SMEs.

Regulatory frameworks

The EMA is responsible for reviewing applications for orphan designation and orphan marketing authorization. If granted, the medicine sponsor will benefit from several incentives, including protocol assistance, protection from competition once on the market and EMA fee reductions - all vital incentives for smaller companies' ability to raise the capital necessary to bring their therapies to patients.

The concept of Unmet Medical Need (UMN) in regulatory considerations has been particularly explored in relation to orphan medicinal products. This concept has become a criterion for eligibility for conditional marketing authorization and accelerated assessments.

UMN definitions are broad and should remain broad to ensure they apply to individual patient needs. Broader definitions are valuable to guide investments in areas with fewer therapeutic options and where scientific developments are more promising. They should not limit patient populations and restrict access to innovations.

Smaller companies are committed to ensuring that medicines reach patients all across Europe. However, launching medicines for rare disease patients is a complex multifactorial process that often goes beyond companies' capabilities and motivation.

Some challenges and critical considerations for market launch include the lack of rare disease patients in that country, delays at the health technology assessment and payer level (including on non-pricing considerations such as efficacy data), country-specific requirements (e.g., the need for pharmacovigilance departments), the lack of specialized care centres able to administer complex new treatments, and many more. For these reasons, launching in all EU Member States is often impossible for smaller companies in the rare disease field. Other solutions to ensure that Europe's patients can access therapies must be sought.

Recommendations

- **Enhance EMA's resources -** to allow for faster and more straightforward orphan designation procedures for smaller companies.

- **Improve international alignment between regulatory agencies, convergency approach -** engage with EMA and U.S. Food and Drug Administration to define and agree on common trial endpoints for market approval.

- **Do not introduce conditionalities for incentives,** such as market launch obligations for all Member States as that would disproportionally hinder smaller companies and European innovation.

- **Revise the EU Cross-Border Healthcare Directive** to ensure European patients can access health care on time.

Market and investment environment

Due to small patient populations, national governments tend to prioritize rare diseases less. As national healthcare structures evolve, new technologies are adopted, public awareness increases, and information is improved, more rare disease patients will be diagnosed, creating additional financial pressure in an already underfunded sector.

With funding under-prioritization and significant uncertainty on reimbursement decisions, rare disease innovation is a very high-risk investment - especially for smaller companies.

Smaller companies face a difficult financial environment and struggle to raise investment from public and private partners to finance their products' research and development. They must have a predictable legal framework to make informed long-term decisions and be able to raise external capital.

In addition, smaller companies do not have the resources to address the EU's market fragmentation fully. Most SMEs do not have the expertise needed to engage with all EU Members States HTA and Pricing and Reimbursement authorities. Furthermore, they have to face a lack of a level playing field because of the use of instruments such as the Advanced Therapy Medicinal Product (ATMP) Hospital Exemption, where the Member States permit the manufacture and use of ATMPs in their territories without fulfilling the requirement to submit a marketing authorization application.

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Recommendations

- **Develop or update national rare diseases strategies to ensure appropriate and continuous funding provisions for rare diseases -** with dedicated opportunities and procedural guidance for SMEs.

- **Develop and implement innovative funding schemes -** explore innovative funding models, including government funding schemes, blended finance, or novel private insurance. Include considerations to accommodate orphan drug effectiveness uncertainty and data generation.

- **Ensure predictability in the legal framework** to maintain and improve investors' confidence with a focus on intellectual property.

- **Promote a multidisciplinary HTA framework** that is evidence-based and allows for better alignment of orphan medicine reimbursement criteria.

- **Promote the alignment of the different national interpretations of hospital exemptions and compassionate use.**

Participating SMEs



National Associations & Bio Regions

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