Overview on Rare diseases and related issues of Orphan Drugs becoming key policy priority.

1. Definitions

Rare disease (RD)

According to the definition adopted by the European Community, a RD is a condition with a very low prevalence of less than 1 in 2000 people. It represents about 30,000 people in Luxembourg. These are very different diseases genetic, chronic and progressive, but they are linked by the same difficulties (lack of therapies, very few drugs and treatments available, lack of information and specific expertise etc..).

Orphan Designation (OD)

This may be granted by the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) at any stage of drug development, provided proper scientific justification of the intended use is submitted. Orphan designation is not an endorsement for the use of the drug for the designated condition. The pharma company shall first submit an application for marketing authorization and the efficacy, safety and quality criteria need to be satisfied.

2. Specificity of RD & OD

The adoption by the European Parliament of the Regulation[1] on Orphan Medical Products and Creation of the Committee for Orphan Medicinal Products (COMP) at the EMA has less than 25 years although some incentives are provided by the EU regulation :

- Market exclusivity in the EU[2]: similar competitive products cannot be placed on the market for 10 years after the granting of marketing authorization[3] and this is extended up to 12 years if performance of pediatric studies.
- Protocol assistance: optimization of drug clinical development aiming at meeting European regulatory requirements by the provision of scientific advice to pharma companies by the EMEA.
- Access to the centralized procedure: application for marketing authorization via a direct access to the EMEA centralized procedure.
- Fee reductions: fee waiver for orphan designation and reduced fees for marketing authorization, inspections, variations and protocol assistance.
- EU-funded research: pharma companies involved in the development of orphan drugs may be eligible for grants from EU and Member State programs and initiatives supporting research and development.
  We may highlight a gap between the protocol assistance and marketing authorisation for an OD which belong to a centralised procedure and the therapeutic value assessment, pricing and reimbursement which are remaining within the realm of Member states' responsibility.

[1] EU Orphan Drugs Regulation 141/2000/EC of the EU Parliament and Council of 16 December 1999 on OMP.
[2] This provision is not applicable if (1) the holder gives his express consent, (2) there are difficulties in supplying the market or (3) the third party can prove that the medicinal product for which he wishes to apply for marketing authorisation is safer, more effective or clinically superior in other respects.
[3] CJUE n° C 138/15 – T 140/12 Case Teva Pharma BV & Case T 80/ 16 Shire Pharmaceuticals Ireland.

Clearly, the orphan drug legislation is developing but RD are still very often tackling the issues of the OD and their availability & affordability.

The gaps between the Member states exclusive competence impacts on the Member states pricing negotiations as for therapeutic value assessment, not all of them have the expertise to perform such evaluations. If at first sight, this exclusive competence can appear as a win-win negotiation for both pharma companies and Member states, the reality is different. Companies may lose part of their ten - year market exclusivity if negotiations are too time consuming and Member states may end up paying high price for the OD due to the reference price negotiated with other countries.

In this context, Luxembourg joined in 2015 the Belgian and Dutch health ministers within BeNeLuxA a joint initiative on drug pricing and reimbursement between the governments (joined after Austria and Ireland), with the aim of giving smaller countries greater negotiating power in discussing drug pricing with international drug firms. The BeNeLuxA initiative aims to make new treatments and so-called orphan drugs available earlier and at an affordable price to patients in participating countries.

Negotiations can be opened with some of the BeNeLuxA's members, not necessarily with all five and the company must be planning to commercialise in all countries participating in the negotiations.
If successful, the price and reimbursement negotiations end up with a joint decision. However, reimbursed prices will not necessarily be identical in each country.

Access to OD may therefore remain difficult due to its pricing and reimbursement.

The adoption of the EUCERD[4] Recommendation on the CAVOMP[5] Information Flow to the European Commission and the Member States is the latest corner stone in the long process of developing and marketing OMPs intended for patients living with rare, heterogeneous, severe and life threatening diseases. The best mechanism for the CAVOMP Information Flow to be implemented at both EU and Member States (MS) levels has been discussed.

Equitable and timely access to approved Orphan Drugs for rare diseases patients remains an issue, and effective market access and utilisation vary strongly between and within Member States.

3. Existence of the National Plan for Rare Diseases (PNMR) for Luxembourg

The PNMR 2018-2022[6] is based on the recommendations of the Council of the European Union in 2009. It was approved by the Government Council on 2 March 2018 around five strategic axes: A transversal vision by the establishment of a governance system for the NRP[7], the improvement of the diagnostic and care pathway through the creation of a referral unit and the

[4] European Union Committee of Experts on Rare Diseases.

[5] Clinical Added Value of OMPs.
[6] https://sante.publique.lu
[7] National Rare Plan

setting up of a team of coordinators, implementing a policy to raise awareness of MR, the development of a multidisciplinary approach.

A National Committee for Rare Diseases has been set up for the entire duration of the plan, in order to implement the PNMR, to monitor its implementation and to propose the strategy for the fight against rare diseases and the result indicators allowing to measure its impact.

4. Europe: a new EU policy framework for rare disease ?

There are many initiatives to converge for a long - term integrated European and national plans, strategies and policies. "*By 2025*[8]*, all countries should have a national plan for rare diseases, with a dedicated multistakeholder oversight body and a dedicated annual budget separated from the global health and social system*".

The EU Court of Auditors Report[9] on the implementation of Directive on Cross-border Healthcare provides an additional impetus for an updated framework for rare diseases by 2023. In its recommendation 3 – Improve support to facilitate rare disease patient's access to healthcare, it provides that "the Commission should: (a) assess the results of the rare disease strategy (including the role of the European Reference Networks) and decide whether this strategy needs to be updated, adapted or replaced". To work towards a simpler structure for any future EU funding to the European Reference Networks and reduce their administrative burden (…)".

The EU Commission plans to evaluate and revise the EU's general legislation on medicines for human use to ensure a future-proof and crisis-resistant medicines regulatory system as part of its EU pharmaceuticals strategy, learning from the COVID-19 pandemic. The aim is clearly to ensure access to affordable medicines, foster innovation, improve security of supply, adapt to new scientific and technological developments. The European Parliament in its Resolution on the EU public health strategy in the post COVID-19 era calls for an action plan for rare diseases at the EU level. Member states such as France, Czech Republic and Sweden have recognized their upcoming presidencies of the EU Council as a platform of discussion to prioritize rare diseases in 2022/2023.

Conclusion: The recent developments in health technology assessments, use of big data and new technologies, pharmaceutical regulations etc… confirm undoubtedly the urgent need to anticipate and include rare diseases in the foresight approach. In Luxembourg, the legislative process in the health sector i.e. the recent Law of 2nd March 2021 creating a National Health Observatory and the ongoing draft of Bill in relation to the future creation of the National Agency for Luxembourg Medicines and Health Products[10] contribute to catch up a past situation which was not favorable to the image of Luxembourg as very often late in the implementation of the EU Directives in this sector. From now on, Luxembourg targets to play a significant role and to be on the map in this sector specially on innovation and tech-health and security which should definitively benefit to the RD and OD hopefully.

[8] This document was prepared as part of the Rare 2030 Foresight Study, under the leadership of EURORDIS-Rare Diseases Europe and with input from all partners. The document should be referenced as follows: Kole, A., Hedley V., et al. (2021) Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today.

[9] Special report 7/2019 EU actions for cross border healthcare (10 April 2019)
[10] Projet de loi n° 7523