efpia

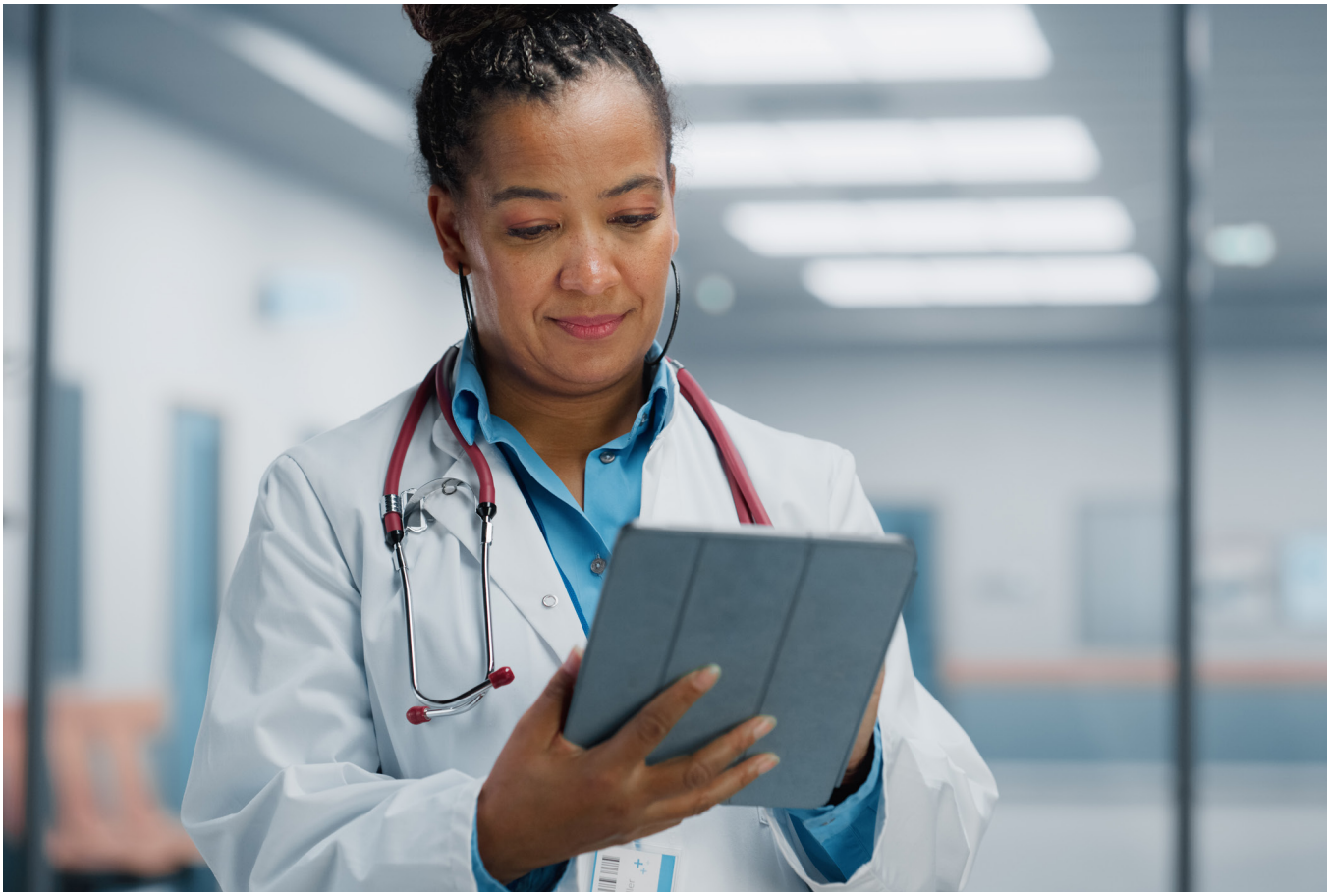
European Federation of Pharmaceutical Industries and Associations

Addressing unmet medical need

October 2023





www.efpia.eu

EXECUTIVE SUMMARY

Addressing an unmet medical need (UMN) is the driving force of the research-based biopharmaceutical industry. EFPIA supports the European Commission's ambition to ensure that EU-level pharmaceutical legislation effectively directs innovation towards UMN. Achieving this commendable goal with no patient left behind requires adopting fit-for-purpose tools that take the evolution of science and patient needs as a starting point, acknowledge the value of innovation, and encourage advances in prevention, treatment and care. That is why EFPIA puts forward a patient-centric, inclusive definition of UMN (any condition that is not adequately prevented, treated or diagnosed by authorised interventions), proposes to strengthen regulatory data protection (RDP) incentives, and asks for active engagement with all relevant stakeholders on the topic of UMN.

1. The UMN definition and its use should be patient-centric and inclusive of different perspectives.

- A broad understanding of UMN should be adopted, so that patients, clinicians, health systems and society's perspectives can be adequately reflected.
- Introducing a UMN definition should not result in the de facto discrimination of patient groups.
- Processes related to the assessment of UMN should be inclusive of all relevant stakeholders, especially patients.
- All stakeholders in the biopharmaceutical ecosystem must be committed to driving innovation to achieve meaningful progress towards addressing UMN.

2. Addressing UMN requires tools that reflect the realities of scientific progress and R&D investment.

- As therapeutic progress is usually achieved through multiple waves, incremental innovation should be incentivised.
- A strong and predictable incentives framework is a prerequisite for R&D investment and subsequent innovation to address UMN.

3. EU action should focus on bolstering the role of Europe as a global leader in innovation – without infringing on Member State competencies.

- The UMN definition should maintain the distinction of roles between EU-level regulators and Member State-level payers.
- The UMN definition at the EU level is not an appropriate tool to tackle access and affordability concerns.
- A restrictive UMN definition coupled with shortened RDP risks eroding European competitiveness vs other regions.

INTRODUCTION

Addressing an unmet medical need (UMN), understood to exist in any condition that is not adequately prevented, treated or diagnosed by authorised interventions, is central to the mission of the research-based biopharmaceutical industry. All research and development (R&D) programmes start from the identification, in a patient-centric and inclusive way, of a UMN coupled with the scientific possibility of addressing it.

The concept of UMN is also used, with varying definitions, throughout medicines' lifecycles and the value chain. For example, it plays a role in:

- Directing public funds for R&D
- Determining eligibility to the European Medicines Agency (EMA) Priority Medicines (PRIME) scheme, accelerated assessment, conditional regulatory approval and orphan designation
- Informing some country-level pricing and reimbursement (P&R) processes.

The current incentives framework (defined broadly as comprising all regulatory facilities, intellectual property (IP) protections and country-level P&R policies) is already tailored to rewarding, and thus incentivising, the development of medicines that deliver the largest benefits to patients, health systems, and society.

The European Commission aims, as part of its revision of the Pharmaceutical Package, to formalise the definition of UMN and to enhance incentives for innovation in areas of UMN. The Commission also proposes to promote competitiveness, ensure better access to medicines, and improve affordability. EFPIA shares the Commission's ambition for Europe to be a global leader in innovation that leaves no patient behind or, in other words, to direct innovation to areas of UMN.

The Commission proposes the introduction of a legislative definition of UMN, paired with the targeting of regulatory resources and modulation of regulatory data protection (RDP) based on this definition (as well as other criteria). The draft definition combines three cumulative criteria:

- Severity of disease ("life-threatening or severely debilitating disease")
- Absence of satisfactory treatment (either no authorised option or disease "associated with a remaining high morbidity or mortality")
- Therapeutic benefit ("meaningful reduction in disease morbidity or mortality").

Products fulfilling all three criteria are to be eligible for a six-month extension of RDP, over a six-year baseline (reduced from eight years currently).

The Commission further puts forward a definition of high UMN (HUMN) specific to orphan medicines, which focuses on the delivery of "exceptional therapeutic advancement" or the absence of an authorised medicine, to grant a one-year extension of orphan market exclusivity (OME) – albeit from a reduced OME baseline of nine years (compared to ten currently).

Introducing a formal and normative definition of UMN at EU level is challenging and will have strong, long-lasting effects on the availability of much-needed treatments for patients across therapeutic areas. The challenge is compounded by the plurality of objectives that the Commission is seeking to achieve through the introduction of a definition of UMN (innovation, competitiveness, access, affordability). Because of the narrowness of the proposed UMN criteria, the choice of incentive (six-month extension of RDP) and the potential impact on country-level payer decision-making, the Commission's current proposal is unlikely to achieve the stated goals. In fact, it runs the significant risk of being counterproductive by decreasing incentives for innovation and slowing down patient access to medicines that have the potential to address UMN.

That is why EFPIA proposes modifications to the proposal, with a view to ensuring that tailored tools are adopted in response to the ambitious goals set and with consideration of the complex, multifactorial nature of the issue. EFPIA's vision for a European legislative framework that helps direct innovation towards UMN centres on the following guiding principles, which are further explored in the rest of this document.

- A patient-centred and inclusive definition of UMN, that takes into consideration the evolution of science and patients' experience of disease, should be adopted. By acknowledging the value of innovation and encouraging advances in prevention, treatment and diagnosis, Europe can ensure that no patient is left behind.
- Strengthened, rather than weakened, incentives should be embraced to bolster the role of Europe as a global centre for innovation.
- All relevant stakeholders should be involved to identify UMN from different perspectives. These multi-stakeholder collaborations should involve representatives from diverse patient groups, as well as broader societal and healthcare system stakeholders (including clinicians). For this purpose, clear rules of engagement should be developed.

1. The UMN definition and its use should be patient-centric and inclusive of different perspectives.

A broad understanding of UMN should be adopted, so that patients, clinicians, health systems and society's perspectives can be adequately reflected.

UMN is a far-reaching concept, with applications across disease areas, geographies and settings. Given this breadth of uses, it is not surprising that there can be significant divergence in how UMN is understood. The concept of UMN is embedded in a medical assessment of the adequacy of the available methods of prevention, diagnosis and treatment. Building on this assessment, perception of UMN varies with the perspective adopted: patient needs usually focus on the impact of disease on their day-to-day lives, clinician needs often link to choice in therapeutic approach, health system needs mostly relate to resource utilisation (in terms of financial resources, personnel, and/or facilities), and societal needs consider productivity and public health concerns (e.g., the "citizen need").

Understanding of UMN is also context specific. In particular, the assessment of UMN linked to regulatory uses or incentives differs significantly from that used in country-level value assessment and P&R processes.

EFPIA proposal:

The definition of UMN, used at EU level for regulatory and incentives purposes, should be revised to holistically reflect all relevant perspectives, especially those of patients.

- **Severity of disease criterion.** UMN should not be misconstrued as pertaining solely to "life threatening or severely debilitating diseases". Many diseases that fit neither of these criteria, including chronic diseases, impose an important burden on patients, carers and society (for example, some cardiovascular diseases, neuropsychiatric diseases, auto-immune diseases).
- **Prevention.** Primary prevention of disease should be recognised as tremendously valuable to patients, health systems and society. The unique aspects of vaccines and vaccination programmes should be recognised within the UMN concept.[1]
- **Patient care.** Patients' desire for therapies that allow improvements beyond morbidity and mortality outcomes, such as therapies that improve quality of life and/or convenience of care, should be adequately reflected. For example, there is an unmet need in paediatric asthma for treatments with formulations, devices and routes of administration that would reduce the burden on patients, caregivers and clinicians.[2]

[1] Please refer to the joint statement by Vaccines Europe, the Active Citizenship Network, the Federation of European Academies of Medicine, and the Spanish Association Against Meningitis for further perspectives on the contribution of vaccines to UMN.

[2] EFPIA & EFGCP. Multi-Stakeholder Workshop on Paediatric Unmet Medical Needs. (2021).

CASE STUDY:
IMPORTANCE OF A PATIENT-CENTRIC DEFINITION OF UNMET NEED FOR MIGRAINE

Limiting the definition of UMN to focus only on life-threatening or severely debilitating diseases risks deprioritising conditions that fit neither of these criteria yet have important negative consequences on patients, carers and society.

For example, migraine is neither life threatening nor severely debilitating for all patients, but it is associated with significant remaining UMN from the perspective of patients, health systems and society. Migraine is a disabling disease that causes temporary incapacity during attacks. It affects patients' quality of life, with almost 80% of patients with migraine also experiencing depression.[3] Migraine is the third most common disease worldwide and affects 41 million adults in Europe (prevalence: 14%) (see Figure 1).[4,5] One study found that migraine is the second leading cause of disability globally and first in young women, with the authors noting that migraine is responsible for more years of lost healthy life in young women than any other disease despite

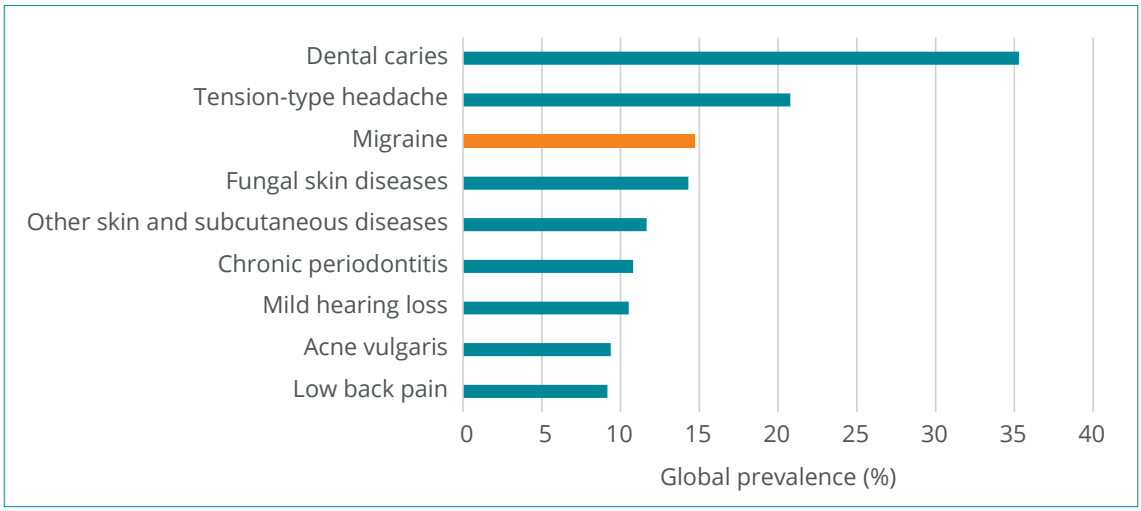


FIGURE 1. Global prevalence of the most common diseases, with migraine being the third-most prevalent[13]

[3] Jahangir, S., Adjepong, D., Al-Shami, H. A. & Malik, B. H. Is There an Association Between Migraine and Major Depressive Disorder? A Narrative Review. *Cureus* (2020).

[4] Agosti, R. Migraine Burden of Disease: From the Patient's Experience to a Socio-Economic View: Supplement Article. *Headache J. Head Face Pain* **58**, 17–32 (2018).

[5] Stovner, L. J., Andrée, C., & On behalf of the Eurolight Steering Committee. Impact of headache in Europe: a review for the Eurolight project. J. *Headache Pain* 9, 139–146 (2008).

[13] Vos, T. et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* **380**, 2163–2196 (2012).

not causing premature mortality.[6] Because patients' productivity is reduced by more than half during attacks,[7] migraine costs Europe an estimated €95 billion in lost productivity every year.[8] The total annual cost of migraine in Europe is estimated to be €111 billion.[9]

Despite the substantial impact of migraine on patients, health systems and society, there remains a significant unmet need. Only 49.2% of people with migraine are professionally diagnosed,[10] which can be attributed to a lack of physician knowledge, stigma associated with the disease and a lack of financial coverage by health systems.[11] In patients who are diagnosed, available treatments present shortcomings. Traditional migraine treatments such as triptans are associated with numerous adverse effects. Calcitonin gene-related peptide inhibitors can prevent migraines with fewer adverse events, but access remains limited.[12] Therefore, a safe, effective and accessible treatment for patients with migraine needs to be developed. Ensuring that the definition of UMN is patient-centric and considers different perspectives would ensure that diseases such as migraine are not deprioritised.

[6] Steiner, T. J., Stovner, L. J., Jensen, R., Uluduz, D. & Katsarava, Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J. *Headache Pain* **21**, 137, s10194-020-01208–0 (2020).

[7] Begasse de Dhaem, O. & Sakai, F. Migraine in the workplace. *eNeurologicalSci 27*, 100408 (2022).

[8] Lancaster University. Migraine costs EU economy €95bn per year. Available here

[9] Linde, M. et al. The cost of headache disorders in Europe: the Eurolight project: Cost of headache in Europe. *Eur. J. Neurol.* **19**, 703–711 (2012).

[10] Yeh, W. Z., Blizzard, L. & Taylor, B. V. What is the actual prevalence of migraine? *Brain Behav.* **8**, e00950 (2018).

[11] EMHA. Call to Action for a comprehensive EU action on migraine. Available here

[12] EMHA. Access to care survey 2021. Available here

Introducing a UMN definition should not result in the de facto discrimination of patient groups.

Whilst the identification of UMN is important to help direct resources to the most pressing areas by signalling their health policy significance, a key risk is that some patients' UMN might be ignored under a narrow definition, resulting in discrimination against certain patient groups. As was highlighted in EFPIA's engagement with patients, the undermining of solidarity across disease areas and possible "competition" to avoid being relegated to "second class diseases" is a key concern.[14]

EFPIA proposal:

- **Patient centricity.** The best way to avoid discrimination across patient groups is to adopt a patient-centric definition of UMN that fairly encompasses the differing needs of all patients. As such, EFPIA proposals presented process related proposals stand to help avoid unwarranted discrimination.

- **Differentiation of 'high' UMN.** No separate category for HUMN for orphan medicines should be created. To incentivise innovation in orphan 'white spots' (i.e., diseases where scientific and economic barriers make innovation particularly difficult), OME should be modulated upwards based on criteria that are both predictable and specific to these white spots: scientifically extremely challenging (less than 0.5 in 10,000 people) or lack of approved therapeutic options. Importantly, progress for patients will require a meaningful strengthening of IP and regulatory incentives (i.e., upwards modulation over a strengthened baseline and accelerated pathways), coupled with actions to bridge the scientific gap (e.g., the Rare Disease Moonshot).[15]

[14] EFPIA. Let's discuss the future of Unmet Medical Needs (UMN) in EU Policies: Report from a multi-stakeholder workshop. Available here

[15] The Rare Disease Moonshot is a joint initiative between EATRIS, ECRIN, the Critical Path Institute, BBMRI-ERIC, EURORDIS, EFPIA, EUCOPE and EuropaBio. The coalition of partners will bring together an ecosystem of rare disease research to explore opportunities for collaboration and support a range of public private partnerships. More information available here

Processes related to the assessment of UMN should be inclusive of all relevant stakeholders, especially patients.

Inclusivity in intent and definition should be matched by inclusivity in process. Refining the legislative frameworks (e.g., guidelines) that specify criteria for the existence of UMNs and decision-making on UMN at product level should rely on the knowledge of those directly affected. As such, legislative provisions should ensure that patients' voices are systematically and fairly incorporated.

EFPIA proposal:

- **Consultation process on the scientific guidelines for UMN.** Article 162 of the proposed European Commission's draft Regulation should be updated to include all relevant stakeholders, including patients and industry, in the consultation process towards defining guidelines on UMN. These scientific guidelines on unmet medical needs should build on a science-based benefit/risk assessment of the product.

- **Product-level assessment of UMN.** The assessment of whether a product seeking marketing authorisation addresses UMN according to the guidelines set should also incorporate the insights of all relevant stakeholders, especially patients.

2. Addressing UMN requires tools that reflect the realities of scientific progress and R&D investment.

As therapeutic progress is usually achieved through multiple waves, incremental innovation should be incentivised.

In many cases, an effective cure (i.e., life expectancy or quality of life on a par with that of the general population) may only be reached through multiple waves of incremental innovation. The advances that have been seen over the last 40 years in highly prevalent and burdensome conditions (such as rheumatoid arthritis and breast cancer) and more recently in smaller populations (such as multiple myeloma) have mostly been achieved through the optimisation of multiple medicines that have not always been perceived as having transformative individual value. This does not mean that the majority of medicines do not have value in their own right, but rather that in most cases, a single wave of innovation is not sufficient to yield a therapeutic option that fully alters the course of disease for all patients.

Incremental innovation should not be seen as opposed to, or less valuable than, breakthrough innovation. Incremental innovation reflects the realities of scientific progress, whereby each new wave leverages increases in understanding of disease pathophysiology and therapeutic mechanism of action enabled by previous waves. There are many examples of important benefits that might be considered as incremental.

- First-in-class products rarely end up being best-in-class ones; progress within a therapeutic class (e.g., on composition) typically helps improve efficacy and safety. These improvements frequently translate into a reduction of the costs associated with the disease, both direct and indirect, derived from factors such as a lower rate of adverse effects, improved efficacy, enhanced adherence, reduced school or work absenteeism for patients, etc.
- A new form or presentation of an existing molecule might deliver faster-acting effects
- Response to treatments varies across patients (i.e., not all patient sub-groups may benefit equally from all new therapies), as well as within a single patient over time. More options in the same indication thus help fill therapeutic gaps.

Overall, incremental improvements result in improved efficacy, quality of life, and safety for patients, savings for health systems, and economic gains for society. In addition, incremental innovation in one disease area might result in positive developments, and even breakthrough innovation, elsewhere. As further investment in a disease may only occur if properly incentivised, the European legislative framework should be designed to reward and encourage both breakthrough and incremental innovation.

EFPIA proposal:

EFPIA welcomes that the UMN definition is not restricted to first-to-market products and provides an avenue for next-in-indication products to demonstrate the benefits they may bring to patients, health systems and society. Nonetheless, the creation of artificial thresholds that prespecify the extent of benefits to be demonstrated should be avoided, so as not to discourage incremental innovation.

CASE STUDY:

INCREMENTAL INNOVATION IN PSORIASIS, MULTIPLE SCLEROSIS, HIV, ADVANCED LUNG CANCER

Psoriasis. Psoriasis is a chronic dermatological autoimmune disease, for which treatments have improved gradually over the past 100 years. Initial treatments included the use of radiation, arsenic and tar, which were associated with high toxicity. Between the 1950s and 1970s, physicians used treatments such as methotrexate, as well as steroids which dramatically suppressed immune system function. In the 1980s, they were replaced by vitamin D ointments, but these were associated with modest success rates and serious side effects. In the early 2000s, TNF-α inhibitors, which were originally developed for the treatment of rheumatoid arthritis but were found to reduce skin lesions in patients with psoriatic arthritis, delivered an improvement of 75% in the severity of psoriasis in about half of the patients. Building on this breakthrough, subsequent biologics (such as IL23 and IL17 inhibitors) developed specifically for psoriasis, achieved much better outcomes. Clinical trials showed that more than 70% of the patients experienced a 90% improvement in the severity of their psoriasis. Thanks to these subsequent waves of discovery and improvement in inhibitor technology, the number of patients with no detectable psoriasis increased from 0.1% with placebo to 4.2% with the first biologic to 40% with current treatments (see Figure 2).[16]

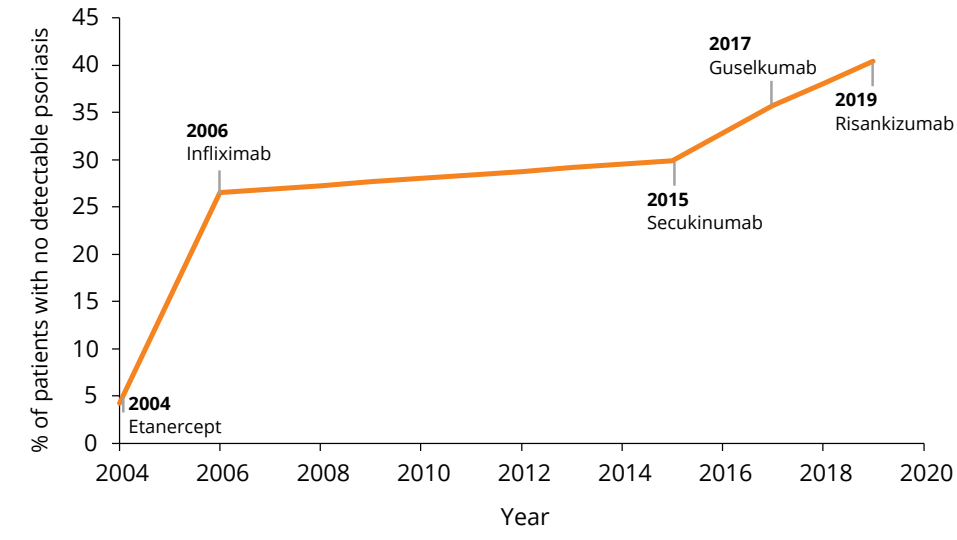


FIGURE 2. Increase in percentage of patients with no detectable psoriasis in relation to new approvals of treatments[19,17]

[16] Armstrong, A. W. et al. Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis. *JAMA Dermatol.* **156**, 258 (2020).

[17] Ahmed, S. S., De, A., Das, S. & Manchanda, Y. Biologics and Biosimilars in Psoriasis. *Indian J. Dermatol.* **68**, 282–295 (2023).

[19] Dadonaite, B. Antiretroviral therapy has saved millions of lives from AIDS and could save more. *Our World In Data* https://ourworldindata.org/art-lives-saved (2019).

12

Multiple sclerosis (MS).

MS is a chronic autoimmune disease that affects the central nervous system. It causes severe disability in patients, often following a relapsing-remitting course in which exacerbations relentlessly reduce the patient's quality of life. Patients with MS require progressively more extensive medical care during exacerbations, increasing demands on caregivers and expenses for healthcare systems.

Initially, patients were treated with immunosuppressants to mitigate the effect of exacerbations. The treatment paradigm has since evolved to include disease-modifying therapies (DMTs), which aim to extend the periods between exacerbations and thus delay disease progression. The first DMT, interferon beta, approved in the US in 1993, delivered a drop in exacerbation rates by 30-40% relative to placebo in clinical studies. This breakthrough marked the first time that a treatment positively affected the course of disease rather than treating its symptoms. Natalizumab, approved in 2004, was shown to be significantly more effective than interferon beta, but its association with a serious side effect (PML) limited its use to patients with high MS disease activity. A wide variety of oral MS treatments received approval in the 2010s, which were as effective as natalizumab but had a much lower risk (if any) of the serious side effect PML. Since the oral treatments have different mechanisms of action, they each have different uses and safety profiles, allowing physicians and patients to select the treatment that is most suitable. Ocrelizumab, approved in 2017, represented another breakthrough in treatment, becoming the first therapy to delay the development of disease disabilities in addition to reducing the number of exacerbations. Nonetheless, ocrelizumab is associated with significant adverse events.

Despite the progressive advances in treatment resulting in dramatic reductions in the number of exacerbations, as shown in Figure 3, it has to date only been possible to delay disease progression, but not stop it. Therefore, there remains a high unmet need for new treatments.[18]

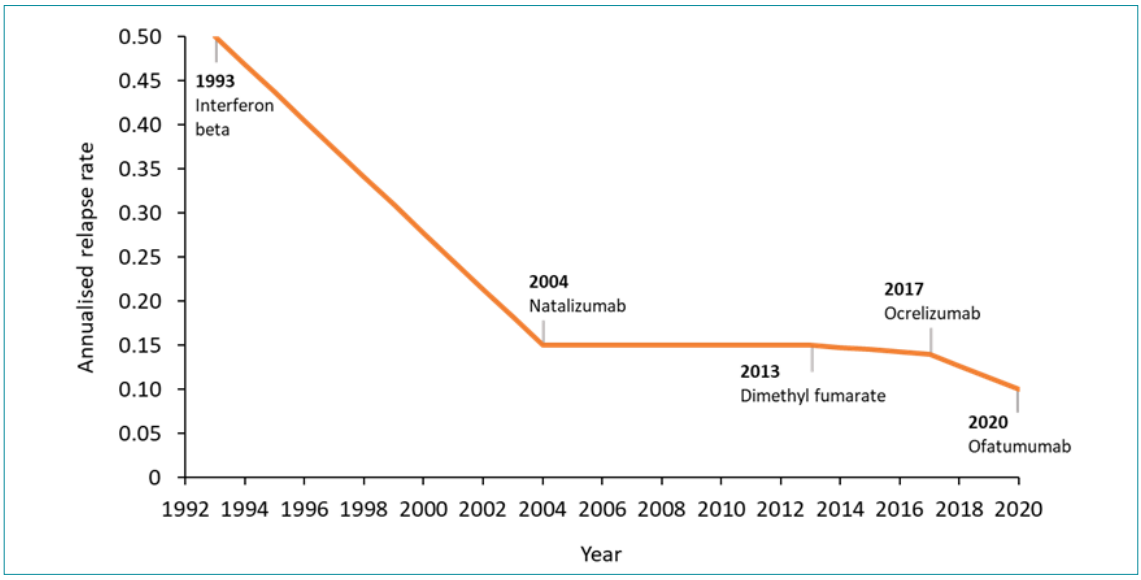


FIGURE 3. Reduction in annualised relapse rate in relation to new approvals of MS treatments.[21]

[18] Yang, J. H., Rempe, T., Whitmire, N., Dunn-Pirio, A. & Graves, J. S. Therapeutic Advances in Multiple Sclerosis. *Front. Neurol.* **13**, 824926 (2022).

[21] EFPIA. Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. (2021). Available here

13

Human immunodeficiency virus (HIV).

HIV is a virus that attacks the body's immune system. The first antiviral drug for HIV, ziduvodin (ZDV, also known as AZT, part of the nucleoside analogues treatment class), was approved by the FDA in 1986. After 1991, several additional nucleoside analogues were added to the arsenal of anti-HIV treatments, as well as a new class of HIV drugs (known as non-nucleoside reverse transcriptase inhibitors) which provided faster activation in blood circulation. The protease inhibitors class was developed next, stopping an already-infected cell from producing more copies of HIV. Most recently, the integrase inhibitors class was developed, which prevent viral DNA from being inserted into host cell DNA, thereby avoiding HIV replication. By 2013, there were six classes of HIV treatments and over 25 approved products. Approval of multiple products within each class helped enhance efficacy and safety profile. Further innovation has come from the combination of multiple therapeutic classes. Waves of innovation over the past 30 years have collectively helped HIV transform from a death sentence into a manageable condition for millions of people (see Figure 4).

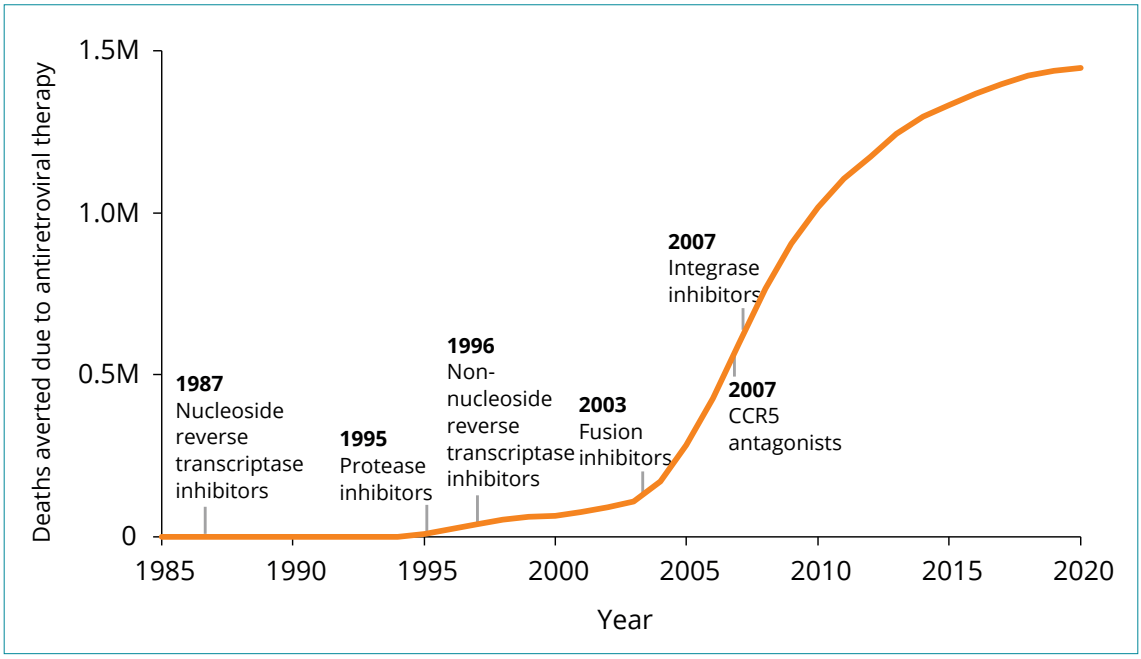


FIGURE 4. Deaths averted due to HIV/AIDS antiretroviral therapy, in relation to new approvals of HIV treatment classes.[19,20]

[19] Dadonaite, B. Antiretroviral therapy has saved millions of lives from AIDS and could save more. *Our World In Data* https://ourworldindata.org/art-lives-saved (2019).

[20] Villaluz, I. & Grantner, G. R. Newly Approved HIV Medications. *US Pharm.* **45**, 7–25 (2020).

A strong and predictable incentives framework is a prerequisite for R&D investment and subsequent innovation to address UMN.

Legislative revisions must reflect not only the realities of science, but also those of the economics that necessarily drive investment decisions. As described in a previous EFPIA publication, scientific, commercial and policy factors coalesce to determine the amount and direction of innovation. IP protections significantly influence the commercial case for investment.[21] Accordingly, the incentives framework described in the Pharmaceutical Package should both provide predictability and clarity at the time of investment and be sufficient in magnitude to justify the risk, time and expense entailed in innovative R&D.

The incentives framework needs to safeguard a strong and vibrant industry in Europe to achieve innovation that fits European needs. UMN is already an important factor in the incentives framework in Europe, playing a role in determining eligibility for PRIME, conditional approval and accelerated assessment. This ensures that treatments addressing areas with unmet needs are prioritised when allocating regulatory resources.

Yet the current proposal makes the system less generous, including for products addressing UMN, with UMN products only guaranteed 6.5 years of RDP compared to eight currently. EFPIA is concerned that proposals put forward by the Commission amount to a significant erosion of baseline RDP, which in itself represents a disincentive for innovation. On the contrary, further incentives are needed to support innovation in areas of UMN.

EFPIA is also wary that a strong emphasis on first-in-class products creates a 'winner-takes-all' situation, with significant consequences for investment decisions, and ultimately potentially devastating impacts on patients. Consider a situation where a pharmaceutical company has invested in a promising product. A second company would likely be disincentivised to invest as a latecomer in another, equally promising, product, for fear that it would not qualify as addressing an UMN if it is approved second in the indication. Because pharmaceutical innovation is very risky, there is a high chance that the first product would fail before reaching marketing authorisation (recent academic literature estimates that only "13.8% of all drug development programmes eventually lead to approval"[22]). Without a competitor product in the pipeline, patients in this situation would be left without a new treatment option for significantly longer.

[21] EFPIA. Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. (2021). Available here

EFPIA proposal:

- **Simplicity.** The language of the definition should be as straightforward as possible, avoiding ambiguity and unnecessary complexity.

- **Value judgements.** The UMN definition should not include value judgements, which cannot be legally defined and introduce significant uncertainty for developers.

- **Modulation of RDP.** Shortening the baseline and varying the duration of RDP will weaken incentives for innovation. In particular, a six-month extension of RDP over a baseline shortened by two years is unlikely to meaningfully shift R&D investment to the areas targeted by the Commission. As such, EFPIA calls for the strengthening of baseline RDP, clear and achievable criteria for upwards modulation of RDP, and an extension of RDP for the products that meet UMN criteria.

[22] Wong CH, Siah KW & Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics.* **20**(2):273-286 (2019).

CASE STUDY: DYNAMICS OF SCIENCE DRIVING INNOVATION WITH MRNA TECHNOLOGY

Scientific factors play an important role in driving innovation. Research aimed at addressing a certain disease area often leads to positive developments, opportunistically, in other areas.

For example, the properties of mRNA in immunology were first discovered in 2005, leading to trials of mRNA-based therapeutics in the field of immuno-oncology in the late 2000s.[23] As the COVID-19 pandemic emerged in 2020, there was an urgent need for an effective, fast and scalable vaccine. Some pharmaceutical companies leveraged the budding mRNA technology towards developing a vaccine.[24] mRNA-based COVID-19 vaccines were developed at unprecedented speed and showed very strong efficacy results. mRNA vaccines were pivotal in the global effort to combat COVID-19, dramatically reducing cases and deaths.[25] Following the COVID-19 success, research is being conducted on the application of mRNA technology in other diseases, with 37 RNA vaccines currently in development in Europe.[26] Early studies have shown that mRNA vaccines can elicit immunity against influenza virus; mRNA vaccines are also being researched in nine other infectious diseases in Europe, including Zika, HIV and rabies. The technology may also benefit non-infectious diseases, with three clinical trials being conducted on mRNA vaccines against cancer in Europe.[27]

[23] Jain, S., Venkataraman, A., Wechsler, M. E. & Peppas, N. A. Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. *Adv. Drug Deliv. Rev.* **179**, 114000 (2021).

[24] Ho, R. J. Y. Warp-Speed Covid-19 Vaccine Development: Beneficiaries of Maturation in Biopharmaceutical Technologies and Public-Private Partnerships. *J. Pharm. Sci.* 110, 615–618 (2021).

[25] Mirtaleb, M. *S. et al.* An insight overview on COVID-19 mRNA vaccines: Advantageous, pharmacology, mechanism of action, and prospective considerations. *Int. Immunopharmacol.* **117**, 109934 (2023).

[26] Vaccines Europe. Vaccines Europe pipeline review 2022. (2023). Available here

[27] Nabel, E. G. & Braunwald, E. A Tale of Coronary Artery Disease and Myocardial Infarction. *N. Engl. J. Med.* **366**, 54–63 (2012).

CASE STUDY: NEED FOR A STRONG INCENTIVE FRAMEWORK FOR CVD TREATMENTS

Cardiovascular diseases (CVD) have seen a steady decline in deaths between 1950 and 2010 thanks to a constant stream of scientific advances (see Figure 5), which collectively led to a ~75% decline in age-adjusted cardiac death rates across the period.[27]

This improvement in patient outcomes was accompanied by health systems savings: without the introduction of medicines from 1995 to 2004, per capita spending on CVD hospitalisations would have been $89, compared to $24 (70% lower) actually spent on medicines.[28]

Nonetheless, there are still UMN in CVD, which continues to be a major cause of death and disability.[29,30] A third of global deaths are due to CVD.[30] Premature deaths due to CVD led to a loss of an estimated 7.1 million working years and €62 billion in productivity across 54 country members of the European Society of Cardiology in 2018.[31]

A strong framework is needed to incentivise the development of treatments aimed at addressing remaining UMN in CVD. However, the Commission's proposal on RDP modulation and definition of UMN may prevent innovation in CVD. The majority of fixed combination medicines approved between 2016 to 2021, which are mostly indicated for CVD, relied on RDP.[31] While there is a significant unmet need in CVD, it is unlikely to meet the proposed UMN definition. This means that IP protection would likely be shortened compared to the current incentives framework. Therefore, Commission proposals may hinder innovation in CVD, resulting in negative outcomes for patients, health systems and society.

[27] Nabel, E. G. & Braunwald, E. A Tale of Coronary Artery Disease and Myocardial Infarction. *N. Engl. J. Med.* **366**, 54–63 (2012).

[28] PhRMA. Prescription Medicines: International Costs in Context. (2017). Available here

[29] CDC. Every Heart Counts. (2021). Available here

[30] Luengo-Fernandez, R. et al. Cardiovascular disease burden due to productivity losses in European Society of Cardiology countries. Eur. Heart J. - *Qual. Care Clin. Outcomes* qcad031 (2023).

[31] IQVIA Institute for Human Data Science. Protection Expiry and Journey into the Market. (2022). Available here

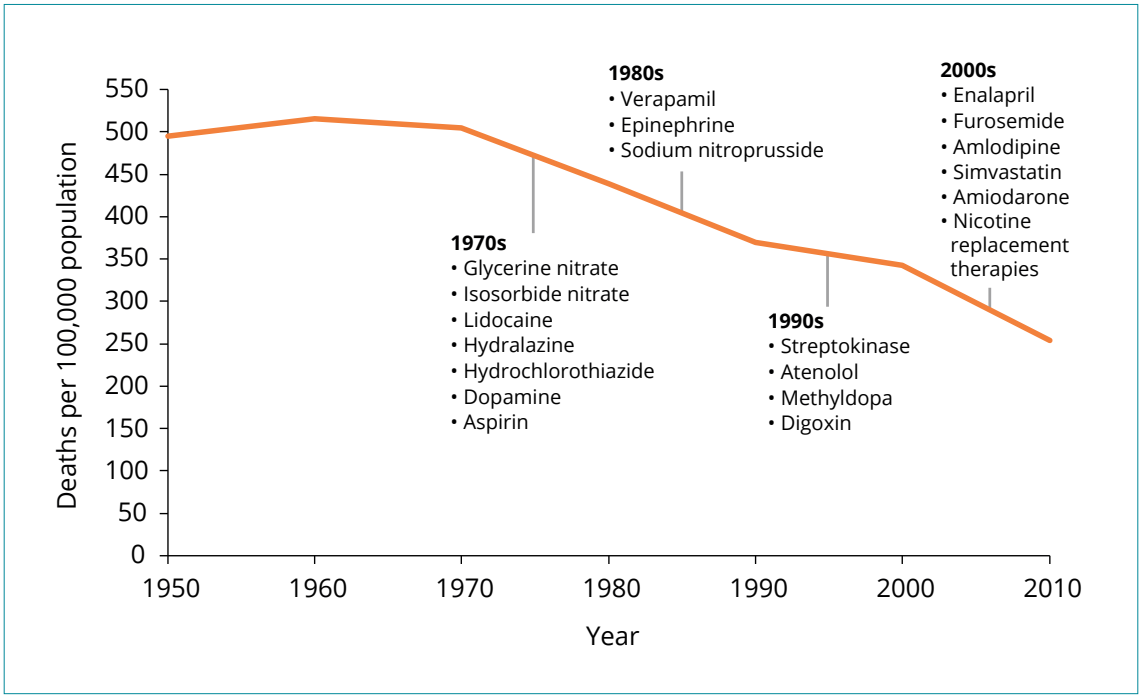


FIGURE 5. Decline in deaths from CVD in relation to treatments added to the WHO Model List of Essential Medicines.[32,33]

[32] NHLBI. NHLBI Fact Book, Fiscal Year 2012. (2012). Available here

[33] Kishore, S. P. et al. Modernizing the World Health Organization List of Essential Medicines for Preventing and Controlling Cardiovascular Diseases. *J. Am. Coll. Cardiol.* **71**, 564–574 (2018).

All stakeholders in the biopharmaceutical ecosystem must be committed to driving innovation to achieve meaningful progress towards addressing UMN.

Because science, economics and policy impediments must all be addressed for innovation to advance, it is necessary for all stakeholders to devise the tailored and dynamic instruments that will collectively foster innovation.

In particular, streamlining regulatory procedures and enhancing support from regulators to developers during the R&D period increases the chance of medicines successfully reaching patients and decreases delays in patient access. As such, gatekeeping access to expedited regulatory pathways according to the patient-centric definition of UMN is an effective and rational way of directing regulatory resources.

EFPIA proposal:

- **Expedited regulatory pathways.** EFPIA supports the Commission's proposal to use the UMN definition to prioritise regulatory resources, including access to PRIME and conditional marketing authorisation.

- **Process inclusivity.** Inclusivity in intent and definition should be matched by inclusivity in process (see process related proposals).

- **Innovation ecosystem.** Progress for patients may only be achieved through concerted action – one example of which is the Rare Disease Moonshot. EFPIA calls on all relevant stakeholders to consider solutions throughout the innovation ecosystem.

3. EU action should focus on bolstering the role of Europe as a global leader in innovation – without infringing on Member State competencies.

The UMN definition should maintain the distinction of roles between EU-level regulators and Member State-level payers.

EU-level consensus on priorities can be beneficial, if done in alignment with the messages presented above. In particular, the EU's added value lies in major initiatives aimed at tackling agreed-upon regional public health priorities (such as antimicrobial resistance, cancer and rare diseases). The EU can help further innovation on a disease-by-disease basis by providing more incentives for addressing UMN and directing regulatory resources accordingly.

Prioritisation between therapies should remain at country level. That is because there are significant variations across EU Member States in terms of societal preferences, epidemiology, burden of disease, standard of care and clinical practice, making it very difficult to reach a common understanding that is reflective of local realities. Member States, through country-level value assessment and P&R frameworks, have extensive tools available to prioritise their resources according to their population's view of UMN.

EFPIA proposal:

- **Risk-benefit profile.** The assessment of UMN by the EMA should take place within the remit of the agency's competencies. The EMA's assessment, in the context of regulatory provisions and at the time of marketing authorisation, should focus on a medicine's risk-benefit profile (i.e., absolute reduction in mortality or morbidity or contribution to patient care) rather than its relative benefits (i.e., comparative efficacy assessment). The EMA's UMN assessment should not automatically be adopted in country-level value assessments, as the assessment of value remains a national competence that reflects local clinical practice, preferences, and frameworks.

- **Use of UMN definition.** Given the separate duties and intent between regulators and payers, the UMN definition should not be linked to country-level P&R processes.

The UMN definition at the EU level is not an appropriate tool to tackle access and affordability concerns.

Access and affordability are fundamental concerns that need to be tackled. However, an EU-level definition of UMN should not be used for such purposes. The definition of UMN should be designed to incentivise R&D activity, which takes place above the national level and should not be affected by country-level considerations of access and affordability. On the other hand, prioritisation of medicines is justified at national level to ensure an efficient allocation of public resources. Hence, access and affordability concerns are best addressed at Member State level, where policymakers and payers have many directly dedicated tools at hand, including the sole control of health spending, cost containment methods and the ability to expand coverage. EFPIA is committed to working in partnership with policymakers and payers to find the right solutions to correctly diagnosed root causes of impaired access.

Shortening baseline RDP duration may not just be ineffective in enhancing access and affordability, but in fact counterproductive. First, a narrow definition of UMN coupled with reduction of incentives is expected to lead to less development of products that can bring important benefits to patients, as the IP framework is taken into consideration at the time of initial investment. Less availability automatically translates to less access. Second, the presence of multiple therapeutic options in a single indication stimulates competition. Brand-on-brand competition (i.e., competition of products still enjoying market protection, ahead of generic or biosimilar entry) contributes to addressing affordability concerns.

EFPIA proposal:

EFPIA has put forward comprehensive proposals to address the root causes of impaired patient access in Europe, which collectively stand to meaningfully improve the breadth and speed of medicine availability across Member States. These proposals include EFPIA companies' Commitment to File in all 27 Member States within two years of marketing authorisation provided that national P&R systems allow and a proposal for an Equity-Based Tiered Pricing. For significant progress to be achieved, Member State policymakers and payers need to enable these initiatives through much-needed changes to local P&R processes.[34]

[34] Please refer to this publication for additional information on EFPIA's access-related proposals

A restrictive UMN definition coupled with shortened RDP risks eroding European competitiveness vs other regions.

EU frameworks play a significant role in ensuring regional competitiveness. In a context of declining dynamism of pharmaceutical R&D in Europe compared to other regions, the revision of the Pharmaceutical Package is a unique opportunity for the Commission to send a powerful signal of Europe's desire to remain a leader in cutting-edge innovation. Conversely, lessening incentives and decreasing flexibility in the regulatory and incentives systems may heighten the industrial decline observed over the past decade.

EFPIA proposal:

Strengthening the incentives framework is essential to hedge against the gradual erosion of European competitiveness observed over the last decade. Baseline RDP should be extended rather than shortened.

CONCLUSION

In conclusion, refinement of legislative provisions relative to UMN proposed by the Commission is needed. The UMN definition and its use should adequately capture the needs of patients, health systems and society, reflect the scientific and economic realities of innovation, and support the ambitious goals of the Pharmaceutical Strategy. EFPIA proposes the adoption of a patient-centric definition of UMN applicable across therapeutic areas that dictates access to dedicated regulatory pathways and is paired with expanded incentives, within a broader ecosystem geared towards supporting innovation.

EFPIA
Leopold Plaza Building ✱ Rue du Trône 108
B–1050 Brussels ✱ Belgium
Tel.: +32 (0)2 626 25 55
www.efpia.eu ✱ info@efpia.eu