White Paper:

driving innovation –

a broad understanding of Unmet medical needs

# Executive summary

As part of the revision of the pharmaceutical legislative framework, the European Commission is considering adopting a more restrictive and criteria-based definition of Unmet Medical Need (UMN) and High Unmet M**edical** Need (HUMN). Maintaining a broad understanding of unmet medical needs has encouraged the research, development and creation of new therapies that otherwise might not have reached patients. EUCOPE believes that **having a restrictive definition** as written in the General Pharmaceutical Legislation (Regulation No 726/2004 and Directive 2001/83/EC) **will have dramatic implications on the pharmaceutical industry, shape long-term research direction and patients’ access to novel therapies.**Including a concept such as **HUMN**  in the Orphan Medicinal Products (OMP) Regulation (Regulation No 141/2001) risks creating a classification of unmet needs, favouring one patient group at the expense of others thereby.

The limited knowledge or understanding of certain medical conditions in the context of rare diseases is a significant challenge for the development of novel therapies. Supporting basic research will help the development of necessary treatments while allowing for enough flexibility in the commercialization of therapies, as opposed to attempting to direct research through UMN definitions. A prescriptive definition of HUMN will not be based on scientific evidence.

There is **no appropriate unifying definition of (H)UMN. An understanding of UMN is based on various factors** such as contexts, stakeholders’ perspectives (e.g. patients, developers, clinicians, regulators, HTA, payers), the objective of the assessments and to whose needs one refers. Several Member States have already outlined their concept of UMN at the national level to inform their health technology assessment (HTA) and pricing and reimbursement (P&R) decisions. Another definition of UMN can lead to a therapy being assessed for UMN on three occasions, with different criteria.

Important **UMNs can still exist among patient groups where there is therapeutic option**. Not all the patients are the same, both across disease areas, but also within the same disease; some might not respond to or benefit from existing therapies, while others may still benefit from further innovation that offers better or more appropriate treatments. Therefore, the absence of a treatment or therapy is not the only unmet need to consider. The quality of life of patients and their families and caregivers, the burden of treatment and the disease and its severity should also be considered in discussions of (high) unmet medical needs. **The concept of UMN is not singular or fixed**, but it evolves over time and changes as the disease progresses and scientifical progress is made.

It is fundamental to recognise the **value of iterative innovation** which can lead to significant improvements for patients. Therefore, EUCOPE warns about including concepts such as ‘cure’ in the definition of UMN. The **concept of ‘curative’** is hard to quantify and assess at the time of marketing authorisation. Linking the concept to an incentive can undermine scientific progress and innovation. Little to no therapies for chronic conditions are currently curative. Improvements in symptomatic treatments can drastically change and improve individual patients' lives. The rise of novel advanced therapies is a sign of change in the healthcare landscape: patients are transitioning from continuous chronic treatment to, in many cases, a one-time treatment with long-term transformative effects.

A **definition of HUMN could lead to a de facto ranking of rare diseases**, which would be arbitrary and detrimental. To date, despite great achievements, treatments available on the market count for only 5% of the estimated 8,000 rare diseases. To drive innovation for the remaining 95%, incentives should look through the lens of investment to **help identify where we need to look for different solutions beyond the legal framework.**, Mostly, this is in the area of basic and translational research where support is lacking. The absence of basic and translational research happens to describe the bulk of the 95% of diseases without an authorised treatment.

EUCOPE supports the Commission’s ambition to promote the development of therapies in areas of (H)UMN. **To achieve this goal in the context of the revision of the General Pharmaceutical Legislation and Orphan Medicinal Products Regulation, EUCOPE recommends**:

1. **Establish a multi-stakeholder dialogue** building on existing EMA and HTA dialogue structures along the drug development path. It should include patient representatives, developers, clinicians, regulators, HTA experts and payers, that can continuously refine and update existing assumptions on unmet needs;
2. The necessary guidance to assess (H)UMN already exists in various EU legislative and non-legislative documents. Therefore, we should **maintain a broad understanding of UMN at EU level** by not further codifying the concept in the General Pharmaceutical, OMP and Pediatric legislation, to encourage continued research for all patient populations who can benefit from therapeutic innovation;
3. **Avoid including the concept of ‘cure’ in any definition or criteria for (H)UMN** as this cannot be fully assessed at the time of marketing authorization and consider disease modifying criteria instead;
4. **Launch an EU-wide rare disease** strategy to support access to and the development of novel therapies, especially in the 95% of rare diseases where no therapeutic options exist;
5. **Modulate Orphan incentives through the lenses of the investment case** rather than through a ranking of unmet needs. This, along with policy initiatives that go beyond the OMP regulation, such as public private partnerships, can help addressing in particular the 95% of rare diseases without an approved treatment.

# 1. What is at stake

The European Union (EU) is undergoing its most significant review of the pharmaceutical legislative framework in two decades. A concept at the heart of these discussions is **unmet medical need (UMN)**, which is relevant to several reviews: the General Pharmaceutical Legislation (Regulation No 726/2004 and Directive 2001/83/EC), the Orphan Medicinal Products Regulation (Regulation No 141/2001), and the Paediatric Products Regulation (Regulation No 1901/2006). EUCOPE understands that the **European Commission is considering adopting a restrictive and criteria-based definition of UMN and highest unmet medical need (HUMN)**. This **would have long-term and significant implications** for the healthcare ecosystem and its stakeholders, in particular patients and the biopharmaceutical industry in both the orphan and non-orphan context.

As a concept, UMN has been widely discussed for many years, across all disease areas and in different medical contexts. As this paper will demonstrate, different understandings of the concept need to exist since they serve different purposes, and are used differently by various stakeholders and reflect the current science and knowledge levels. The planned reviews would shape how EU institutions define and understand UMN for the purpose of rewarding innovation through regulatory incentives and support. The agreed understanding and criteria used to determine UMN will:

* Inform pharmaceutical companies research and development (R&D) programmes;
* Shape developers’ commercialization decisions;
* Inform how society assesses the value of therapies;
* Inform health priorities and at an extreme level which patients groups will, and will not, benefit from possible new therapies and technologies for the coming decades.

# 2. Lack of consensus on UMN

The concept of UMN seems clear upon first reflection, but, the discussion becomes significantly more complex when attempting to codify UMN and establish a definition that appropriately captures the diversity that exists.

The concept of UMN is not singular, binary nor fixed. It can and does evolve over time, and is also shaped by the specific stakeholder’s perspective. The common understanding of UMN should be sufficiently flexible to ensure that it keeps pace with scientific progress and reflects local needs. A rigid or insufficiently broad understanding of UMN will overlook the needs of diverse patient groups, and risks creating artificial areas of unmet need. **This will have practical implications for where research is undertaken and for whom, new therapies are developed.**

**RECOMMENDATION 1:** **Establish a multi-stakeholder dialogue building on existing EMA and HTA dialogue structures along the drug development path, that includes patient representatives, developers, clinicians, regulators, HTA experts and payers, that can continuously refine and update existing assumptions on unmet needs.**

*Different interpretations of UMN and stakeholder perspectives*

How one understands UMN depends on the context, the objective of the assessment, the stakeholders’ perspectives (e.g. patients, developers, clinicians, regulators, HTA, payers), whose needs one refers to (e.g. individual or societal), and its changes over time as the disease progresses or scientific progress is made. A literature review with an international scope revealed **over 15 different definitions of UMN**, which included different criteria or elements[[1]](#footnote-2).

The concept of UMN may be formally or informally incorporated in decisions at national level in several Member States to inform their health technology assessment (HTA) and pricing and reimbursement (P&R) decisions. Below are examples of what some Member States look for when assessing UMN:**RECOMMENDATION 2: The necessary guidance to assess (H)UMN already exists in various EU legislative and non-legislative documents. Therefore, we should maintain a broad understanding of UMN at EU level by not further codifying the concept in the General Pharmaceutical, OMP and Pediatric legislation, to encourage continued research for all patient populations who can benefit from therapeutic innovation.**

**Table 1: Examples of the UMN concepts at national level**

Italy

* To receive ‘innovative status’ and the incentives linked to this designation, developers must demonstrate “maximum or important level of therapeutic need”, which is a proxy for UMN. Criteria for innovative status are outlined in Resolution No. 1535/2017, Annex 1.

France

* HAS’ 2022 ASRM methodology ([Transparency Committee doctrine](https://www.has-sante.fr/upload/docs/application/pdf/2021-03/doctrine_ct.pdf)) includes specific factors, including disease prevalence.
* AAP (autorisation d’accès précoce) (successor of the ATU (Autorisation Temporaire d'Utilisation) scheme for pre-authorization products) is meant to accelerate patient access to promising medicines not yet covered by a marketing authorisation in France, particularly in areas of recognised UMN. To achieve faster access, promising medicines are made available through the EAP before they are granted European Medicines Agency marketing authorisation and before an HTA reimbursement decision is made.

Belgium

* Federal legislation (2014/22066, Article 5) outlines the necessary criteria for a therapy to be considered an UMN in the context of reimbursement decisions.

*All patients deserve to benefit from continued technological innovation*

Although patients might benefit from an existing treatment, they might still benefit from future innovation built on research and development programmes that yield better outcomes by reducing the disease or treatment burden. One approved treatment does not necessarily alleviate all UMNs. Continued innovation and development as in the case of rare blood cancers, such as myeloproliferative neoplasms (MPN), has ensured that patients can be treated with less complications and side events, thus, leading to higher quality of life and higher life expectancy[[2]](#footnote-3). Similarly, in the area of multiple myeloma, continued development of treatments has increased median survival from 2-3 years 20 years ago, to over 10 years with long-term durable remissions in an increasing proportion of patients[[3]](#footnote-4). Yet, UMN continues to exist. Research and development must continue for these patients and should not stop at the first treatment. Competition between different therapeutic approaches helps patients and drives innovation. Diversity in treatment options provides healthcare professionals with a variety of viable treatment options that reflect the needs of the patient. If the first direct acting anti-viral in **Hepatitis C** had been considered to fully address an UMN, the development of pan-genotypic treatment regimens (acting against every genotype) would not have been developed. Continued innovation not only provided novel therapeutic solutions for patients, but helped reduce the price of anti-viral therapies. The same would apply to patients who are refractory to or intolerant of first-line antibiotics/antifungals and may need use of reserve antimicrobials to treat life-threatening infections.

In addition to the availability criteria of a treatment, there are **several other important factors that should be considered** when discussing UMN, including disease severity, burden of illness, burden of treatment, mortality, existence of a satisfactory treatment (e.g. only symptomatic treatments available, etc.), quality of life, and indirect impact on families and caregivers. These factors are especially important in the **rare disease context** and when reflecting on scientific and technological value. The development of a treatment that addresses the underlying cause of the condition, or a cell or gene therapy is an important and transformative milestone. However, the emergence of a symptomatic treatment where no previous therapy existed also represents a major step forward. Both types of interventions can represent important developments to the people’s lives, as well as those of their families and caregivers. These cases demonstrate the importance of reflecting on the patient experience, and ensuring that the patients are placed at the centre of a discussion around UMN is essential.

**Ultimately, UMN is not a static concept**  **and evolves over time**. As new therapies are developed and our understanding of the disease improves, different disease areas might become more straightforward to treat, signalling a shift in where research is needed and UMN exists. The emergence of new technologies such as advanced therapy medicinal products (ATMPs) offers previously unimaginable treatment options. External factors also shape UMN discussions. The COVID-19 pandemic illustrated the need for more research in pandemic preparedness, and climate change will allow for diseases to spread to new geographic regions.

The driving force behind UMNs also differs based on the therapy area and the patient community being discussed. As illustrated when considering rare diseases, neglected tropical diseases, antimicrobial resistance (AMR), and chronic conditions such as neurology, there are different reasons why UMNs exist. Adopting a **strict EU interpretation of UMN will overlook important elements and causes of UMN,** **and prevent the Commission from achieving its goal of encouraging innovation in areas where no or only a few therapeutic options are available**.

# 3. possible Implications of the legislative review

An EU definition of UMN would have significant implications on public health and the pharmaceutical industry’s R&D investment in the EU. A definition would impact therapies under development and authorized therapies by shaping patient access to novel therapies, the direction of R&D, and value assessment and P&R decisions.

*Tension between science and research and UMN definitions*

The fundamental challenge in developing novel therapies in the context of rare diseases (as well as other lesser understood chronic disease areas including neurology) is the lack of knowledge or understanding of the conditions. This can be due to the rarity, mortality, limited understanding of or complexity of human genetics and the biological processes in question, meaning there is insufficient understanding of the disease, its drivers, and how to provide symptomatic relief or appropriate treatment.

The development of a novel therapy takes on average 10 years[[4]](#footnote-5),[[5]](#footnote-6), excluding the basic and pre-clinical research that might be required to gain a better understanding of the disease area and modes of action of the possible intervention, which will add additional years to the development process. **The combination of new technologies emerging over time that were previously out of reach and a long development timeline for novel therapies will make it difficult for policies around UMN to respond appropriately to drive research where it is urgently needed without disincentivising research investments**.

*Pricing Pressures*

A driving factor informing a developer’s decision to commercialise a therapy is the commercial viability of the product and the existence of a business case. As outlined in the 2022 report commissioned by the Dutch Ministry of Health, t*he financial ecosystem of pharmaceutical R&D: an evidence base to inform further dialogue*, in our current economic system, expected financial return ultimately determines if a product will be launched[[6]](#footnote-7). While more effort can be made to coordinate and signal the willingness to pay from Member States, this should not be done by means of the pharmaceutical and OMP incentives revision. Global price signals are an important pull factor in informing research priorities, regulatory submissions and product launches. If common incentives at EU level are adapted to drive research in specific directions, it risks narrowing the scope of innovation made available in the EU.

An assessment of UMN often already takes place at Member State level with national HTA bodies and payers including UMN in their own assessment criteria. This is further complicated by the fact that Member States and their assessment bodies can interpret UMN differently. The varying interpretations of UMN at EU and Member State level already create barriers for developers in the current system (e.g. products that receive CMA can face hurdles to demonstrate they address an unmet need at P&R stage). A definition in EU legislation could lead to a situation where UMN is assessed at least twice, at EU and National level, or even a third time through the EU HTA process. Such an approach would have the effect of creating a list of indications for which therapies are less likely to be developed as they are signalled to be less commercially viable.

Rather than magnifying the impact of pricing considerations in driving R&D decisions, which can discourage R&D in other important areas, more coordinated pricing signposting and dialogue with industry through horizon scanning programmes should be pursued. This will allow Member States to articulate priorities to developers at early stages, while continuing to encourage innovation in a broader range of indications.

*Application of UMN in the EU context*

A narrower interpretation of UMN at EU level is not needed to direct innovation, as the concept of UMN already exists in the EU’s legislative framework (see annex 1). Recognising the fact that there are different drivers of UMN, the EU’s legislative framework has established different pathways and incentives to drive innovation and this diversity and inherent flexibility needs to remain in the system.

The different interpretations touch on concepts ranging from population size to diseases severity and availability of authorised therapeutic options. The review of the pharmaceutical legislation should build on and maintain the scope of the existing legislative tools in identifying UMNs.

**RECOMMENDATION 3:** **Avoid including the concept of ‘cure’ in any criteria for (H)UMN as this cannot be fully assessed at the time of marketing authorization and consider disease modifying criteria instead.**

*Concept of ‘cure’ should not be included in a common understanding of UMN*

When discussing innovation and different levels of unmet need, it is important to consider breakthrough innovation, as well as other elements, including **incremental innovation**. While there have been huge advances in science that effectively eradicated previously incurable diseases and this scientific progress continues, **there is a significant danger in referring to concepts such as ‘cure’ in a definition of UMN**. Improvements in symptomatic treatment can have major benefits for patients.

The concept of ‘cure’ or ‘curative’ is hard to quantify, and is often built on continued and step-wise research. Few to no therapies for chronic conditions are currently curative, and it would be infeasible to conclusively demonstrate the curative nature of a treatment to the levels required by payers and HTA bodies before Marketing Authorisation. Challenges already exist in adapting their assessment methods and pricing models to reflect the long-term benefits of novel therapies such as cell and gene therapies due to their inherent data uncertainties. While post-authorisation evidence collection is key, it would be unrealistic to follow a patient for the duration of their life before submitting a Marketing Authorisation in order to establish a possible ‘curative’ nature of a therapy to the satisfaction of regulators, payers, and HTA bodies[[7]](#footnote-8).

The development of a hypothetical ‘curative’ therapy or a treatment with a curative potential, does not happen as an immediate and logical consequence of developing a symptomatic treatment. Significant and continued investment and research is needed to continue to improve health outcomes and expanding our understanding of disease areas. This continued innovation must not be discouraged or disincentivized. A perverse incentive and focus on ‘cures’ without considering all the intermediary research risks undermining the Commission’s aim and fails to recognise the reality of medical innovation.

Several important breakthroughs have taken place over the past two decades, such as the development and launch of transformative cell and gene therapies, and the fastest ever development and commercialisation of a vaccine in response to the COVID pandemic[[8]](#footnote-9). However, these developments built on the research and accomplishments of previous endeavours. The **development of novel therapies is stepwise and incremental**. The work and research in the area of liquid nano-particles (LNP) over the past decade played a key role in the development of mRNA vaccines in response to the COVID-19 pandemic. Building on mRNA and years of scientific research in other fields, governments and research are now aiming to develop vaccines to new COVID-19 strains or future pandemics within 100 days[[9]](#footnote-10). This incredible response is possible due to years of research, some of which might not have had a direct link to vaccine development initially.

# 4. UMN in the orphan context

**RECOMMENDATION 4:** **Launch an EU-wide rare disease strategy to support access to and development of novel therapies, especially in the 95% of rare diseases where no therapeutic options exist.**

*A definition of highest unmet medical needs would be detrimental to patients and developers*

The Orphan Medicinal Products (OMP) Regulation has helped overcome an existing market failure and contributed to the development and authorisation of about 200 therapies in the past 22 years[[10]](#footnote-11). Despite this progress, treatments are available for only 5% of the estimated 8,000 rare diseases.

As recognised by the European Commission on various instances, all orphan and paediatric indications can be considered as addressing an UMN. However, EUCOPE understands that the European Commission is thinking of including an additional concept in the OMP Regulation, that of **highest unmet medical need (HUMN). Such a concept would de facto create** a superficial ranking among rare diseases.

*The current OMP Regulation already include balanced and effective tools to address patient needs*

In the current version of the OMP Regulation, Article 3 refers to the life-threatening or chronically debilitating nature of the condition as a requirement for orphan designation of a medicine. Unmet needs are implicit in the ‘Significant Benefit’ criteria for designation. This approach should be maintained in the review of the OMP Regulation, instead of creating another layer of ‘highest’ unmet medical needs as the test of ‘significant benefit’. The current system takes into account the evolution of therapeutic options and the heterogeneity of patient populations.

*No patient is the same*

The understanding of what is an unmet need changes and evolves over time, based on current best practices and available treatments. It also varies profoundly from one patient to another, given that no two patients are the same, certainly across disease areas, but also within the same disease. This is true for all patients and even more evident in rare disease. An example of this is cystic fibrosis, a genetic disease caused by mutations, or errors, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. About 2,000 CFTR mutations have been identified, most are very rare, and occur in only a few families. Conventionally, these mutations are sorted into six classes based on their effects on the protein structure and function. The heterogeneity in cystic fibrosis means that not all mutations in the same class respond to the same drug. Conversely, sometimes mutations in different classes could be targeted by the same treatment.[[11]](#footnote-12)

*A HUMN definition would not capture the societal aspects of unmet needs*

While crucial, the absence of treatment is not the only unmet need to consider. Disease severity, burden of illness and impact on the quality of life of patients, as well as the significant indirect costs for families and caregivers can also qualify as high unmet needs. For instance, in the case of Phenylketonuria (PKU), a genetic disorder that results in decreased metabolism of the amino acid phenylalanine, a dietary treatment does exist and can be quite effective to treat the disease. However, it is difficult to adhere to, thus creating a burden for patients and families thus leaving still significant unmet needs.

**A legally binding definition of HUMN would not be evidence-based**, since some rare diseases progress rapidly and have fatal effects at the early stage or progress slowly and have high burden of disease towards adulthood. It would risk creating further discrimination and possibly inequalities among patient groups. Similarly to what is mentioned for unmet medical needs in the general pharmaceutical framework, including criteria such as **‘curative’** in a definition of highest unmet medical need would prove unfeasible due to the lack of data and **uncertainty in making such assessment at time of marketing authorisation.**

*Modulation should NOT be based on a restrictive definition of HUMN*

Beyond the debate on the definition as such, it is important to assess the impact of a HUMN definition in legislation.

We understand from some of the Commission’s planned proposals that a definition of HUMN would serve as key criterion to modulate orphan incentives (i.e. market exclusivity or novel incentives provided by the Regulation). HUMN would serve as an identifier for a product meriting the highest level of incentives and therefore also influence the investment and development decisions on other orphan products. This, in the intention of the Commission, would steer investment towards the 95% of diseases without an authorised therapeutic option.

However, we don’t believe that the abovementioned proposal will achieve the intended goal. Extensive consultation with our membership and the joint work with the patient group EURORDIS, and the expert of the Expert Group on Orphan Drug Incentives (OD Expert Group), led us to the conclusion that, in applying a modulation approach, it would be more effective to use other identifiers to encourage research in the missing 95% rather than basing the level of incentives on a restrictive definition of HUMN. In particular, the group developed a model of incentives based on the ‘investment case’ of an OMP (see next paragraph).

**RECOMMENDATION 5:** **Modulate Orphan incentives through the lens of the probability of success i.e. the investment case, rather than through a ranking of unmet needs. This, along with policy initiatives that go beyond the OMP regulation, such as public private partnerships, can help addressing in particular the 95% of rare diseases without an approved treatment.**

Modulation of the market exclusivity awarded to orphan therapies should be based on the investment case for conducting research and development of a specific therapy for rare disease or disease area. Rather than attempt to ‘rank’ unmet medical needs, that exist across the whole spectrum of rare diseases.

The approach developed by the OD Expert Group proposes to modulate incentives on the basis of the following criteria:

1. Some development-ready research exists but no product is yet on the market = increase the level of incentives
2. Development projects for which there is disease knowledge and some research activity but no established market, e.g. some sub-populations are underserved or the product is a new technology/MoA = maintain the current level of incentives
3. Development projects for which there is already an established market, e.g., more than three products addressing the same rare disease’ subpopulation = carefully decrease incentives, yet not discouraging innovation in these areas in the long run

*The rationale of the investment case approach*

By categorising OMP development projects into one of the three categories based on their cumulative risks along the development path, just enough incentives and support are provided to make the investment case for each project positive. This route will promote the development of medicines in a cost-effective way, while having the flexibility to meet evolving patient needs, as it does not require defining and updating the concept of unmet needs as innovation in rare diseases continues to grow.

Looking at incentives through the lens of investment also **helps to identify where we need to look for different solutions beyond the legal framework.** The absence of basic and translational research, happens to describe the bulk of the 95% of diseases without an authorised treatment that the Commission aims to address with its OMP incentive review.

# 5. eucope recommendations

EUCOPE supports the Commission’s intension to promote the development of therapies to support patients with unmet medical needs. The approach currently being pursued by the Commission risks bringing about unintended consequences while not fully addressing the challenges faced in the areas of (H)UMN. This change will have implications for any and all diseases and treatments, both in the orphan and non-orphan context. Therefore, EUCOPE proposes the following policy asks to address (H)UMN, especially in the context of the ongoing legislative reviews:

1. Establish a multi-stakeholder dialogue building on existing EMA and HTA dialogue structures along the drug development path. This includes patient representatives, developers, clinicians, regulators, HTA experts and payers, that can continuously refine and update existing assumptions on unmet needs;
2. The necessary guidance to assess (H)UMN already exists in various EU legislative and non-legislative documents. Therefore, we should maintain a broad understanding of UMN at EU level by not further codifying the concept in the General Pharmaceutical, OMP and Pediatric legislation, to encourage continued research for all patient populations who can benefit from therapeutic innovation;

Pharmaceutical strategy

1. Avoid including the concept of ‘cure’ in any criteria for (H)UMN as this cannot be fully assessed at the time of marketing authorization and consider disease modifying criteria instead;
2. Launch an EU-wide rare disease strategy to support access to and development of novel therapies, especially in the 95% of rare diseases where no therapeutic options exist;

Rare diseases

1. Modulate Orphan incentives through the lens of the probability of success i.e. the investment case, rather than through a ranking of unmet needs. This, along with policy initiatives that go beyond the OMP regulation, such as public private partnerships, can help addressing in particular the 95% of rare diseases without an approved treatment.

**Annex 1: References to the concepts defining or referring to UMN in the current EU pharmaceutical acquis**

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| --- | --- | --- | --- |
| Definition | Legislation | Criteria | Objective |
| Unmet medical needs | Regulation (EC) No 726/2004 - Article 14-a | -**no satisfactory method of diagnosis, prevention or treatment in the Union or,**  -even if such a method exists, the medicinal product concerned will be of major therapeutic advantage | Grant conditional marketing authorisation |
| Significant clinical benefit | Regulation (EC) No 726/2004, Art 14(11) and Directive 2001/83/EC - Art 10(1)  Specified in [guidance [link]](https://health.ec.europa.eu/system/files/2016-11/guideline_14-11-2007_en_0.pdf) | -**relevant advantage or major contribution to patient care**.  **-demonstration of greater efficacy,**  **-improved safety profile,**  **-and/or more favourable pharmacokinetic properties resulting in demonstrable clinical advantage**s compared to existing methods. | Grant +1 year of market protection for developing a new indication |
| Major therapeutic advantage | Regulation (EC) No 507/2006, Art 4(2)  Specified in guidance  [[link]](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-scientific-application-practical-arrangements-necessary-implement-commission/2006-conditional-marketing-authorisation-medicinal-products-human-use-f_en.pdf) | -**Meaningful improvement** of efficacy (or clinical safety), such as having an impact on the **onset and duration of the condition**,  -or **improving the morbidity or mortality of the disease**. | Primarily in relation to the definition of unmet medical need for the purpose of granting conditional marketing authorization.  The definition is used also in various EC and EMA guidance to assess the impact of the treatment on a condition. |
| Significant benefit (Orphan) | Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03) | ‘a clinically relevant advantage’ may be based on:  — **improved efficacy for the entire population** suffering from the condition **or a particular population subset** or a subset that is resistant to the existing treatments; or  — **a better safety profile or a better tolerability for the entire population** suffering from the condition or for a **particular subset**.  ‘a major contribution to patient care’ may be based on:  — **ease of self-administration**, e.g. if the new treatment allows ambulatory treatment instead of treatment in a hospital only or if it has a significant impact on convenience of use and reduces treatment burden;  or — **significantly improved adherence** to treatment due to a change in pharmaceutical form | Obtain orphan designation and maintain it if confirmed at time of marketing authorisation |
| Major public health interest | Regulation (EC) No 726/2004, Art 14(9) | EMA recognises that there is no single definition of what constitutes major public health interest; each individual situation should be justified by the Applicant and will be assessed by the CHMP on a case-by-case basis.  There are also criteria to define public health emergency in the Decision 1082/2013/EU Art.12 | Accelerated assessment |
| EU HTA | Regulation(EU) 2021/2282, Art 7 (4)(a), Art 17(3)(a) | Although the EU HTA Regulation does not include a new definition of unmet medical needs, EUnetHTA 21 is developing more guidance on the below selection criteria:   1. Unmet medical needs (no treatment or only unsatisfactory treatment available) (def of Regulation (EC) No 726/2004 – see above) 2. first in class; 3. potential impact on patients, public health, or healthcare systems; 4. significant cross-border dimension; 5. major union-wide added value; 6. union clinical research priorities. | Products to be selected to receive Joint Scientific Consultation |
| PRIME | The scheme is not established under EU legislation, but is an excellent example of the flexibility allotted to the EMA to address the needs of the healthcare community and fill existing needs. | The EMA uses the same interpretation of UMN used for a product to be eligible for Conditional Marketing Authorisation, and must demonstrate this benefit by means of early clinical data[[12]](#footnote-13) | Eligibility for PRIME a priority review scheme set to speed up the development of medicines that could potentially address an unmet medical need. |
| Paediatric Products Regulation | Regulation (EC) No 1901/2006, Art 43 | **The prevalence** of the conditions in the paediatric population,  **The seriousness** of the conditions to be treated,  **The availability and suitability of alternative treatments** for the conditions in the paediatric population, including the efficacy and the adverse reaction profile of those treatments, including any unique paediatric safety issues. | Identify paediatric research priorities |

1. https://www.clinicalleader.com/doc/what-s-in-a-name-understanding-unmet-medical-need-may-help-align-prioritization-strategies-0001 [↑](#footnote-ref-2)
2. https://www.sciencedirect.com/science/article/abs/pii/S2352302620303732 [↑](#footnote-ref-3)
3. <https://www.onclive.com/view/innovation-fuels-survival-gains-in-multiple-myeloma> [↑](#footnote-ref-4)
4. http://phrma-docs.phrma.org/sites/default/files/pdf/rd\_brochure\_022307.pdf [↑](#footnote-ref-5)
5. https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms [↑](#footnote-ref-6)
6. Kalindjian et al. (2022) The financial ecosystem of pharmaceutical R&D: an evidence base to inform further dialogue.https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/rapporten/2022/02/28/the-financial-ecosystem-of-pharmaceutical-rd/the-financial-ecosystem-of-pharmaceutical-rd.pdf. Accessed 24 June 2022 [↑](#footnote-ref-7)
7. EUCOPE Position Paper on RWE across the Life-Cycle of Cell and Gene Therapies – include when finished [↑](#footnote-ref-8)
8. https://www.mckinsey.com/industries/life-sciences/our-insights/fast-forward-will-the-speed-of-covid-19-vaccine-development-reset-industry-norms [↑](#footnote-ref-9)
9. https://www.gavi.org/vaccineswork/why-world-set-getting-next-pandemic-vaccine-out-just-100-days [↑](#footnote-ref-10)
10. https://od-expertgroup.eu/wp-content/uploads/2021/06/european-expert-group-on-orphan-drug-incentives-report.pdf [↑](#footnote-ref-11)
11. https://www.nature.com/articles/d41586-020-02106-w [↑](#footnote-ref-12)
12. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines [↑](#footnote-ref-13)