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European Federation of Pharmaceutical Industries and Associations

The Commission's criteria to define unmet medical need and high unmet medical need

Implications of a proposed incentive framework

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KEY POINTS

1. The EC has proposed a provisional set of criteria to define unmet medical need (UMN) and high unmet medical need (HUMN) in the revised Directive and Regulation, respectively;

2. While some criteria are clear and comprehendible, others are ambiguous and increase uncertainty for medicine developers;

3. In therapeutic areas that generally rely on incremental innovation to improve patient outcomes, the currently proposed criteria would likely not recognise these much-needed innovations as fulfilling a UMN;

4. The current EC approach, as formulated in the proposed legislation, could impede the EC's goal to direct innovation to areas in which UMNs exist from a patient and healthcare perspective

5. The dialogue within the EU around the definition of (H)UMN and the formulation of criteria should be informed by:

   a) a multi-stakeholder discussion where diverse perspectives are incorporated;

   b) a sound analysis of historic cases as well as assessments of products that are currently in the development pipeline to understand how such a definition will impact pharmaceutical development pipelines and selection of candidates going forward;

   c) a sound analysis of which factors are also important to achieve the EC's intent to direct innovation to areas in which UMNs exist.

BACKGROUND

As part of the revision of the pharmaceutical legislation, the European Commission (EC) is planning for a broadly applicable definition of unmet medical need (UMN), that will be integrated in the legislation and form the basis for access to some expedited regulatory pathways and a partial recovery of a period from generally reduced regulatory data protection. The Commission's goal for this definition is to better direct innovation towards areas of UMN, while at the same time addressing availability, access, and affordability challenges. To this end, the EC has proposed a provisional set of criteria to define UMN in Article 83 of the revised Directive (see Box 1).

BOX 1: ARTICLE 83 (DIRECTIVE): MEDICINAL PRODUCTS ADDRESSING AN UNMET MEDICAL NEED

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. Designated orphan medicinal products (…) shall be considered as addressing an unmet medical need.

The proposed definition of UMN points out that "designated orphan medicinal products (…) shall be considered as addressing an unmet medical need" and are assessed by a different set of criteria to define high unmet medical need (HUMN) in the proposed Regulation (see Article 63, Criteria for orphan designation). These criteria are similar to those put forward in the Directive for defining UMN, with the exception that the applicant needs to demonstrate that the orphan medicinal product, in addition to having a 'significant benefit', will bring 'exceptional therapeutic advancement' if there is already another medicinal product authorised for such condition (see Box 2).

BOX 2: **ARTICLE 70 (REGULATION): ORPHAN MEDICINAL PRODUCTS ADDRESSING A HIGH UNMET MEDICAL NEED**

1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:

a) there is no medicinal product authorised in the Union for such condition or where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement;

b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

Although it remains unclear how exactly the proposed criteria for defining UMN and HUMN will be applied in practice and how they will be implemented in regulatory pathways, it is nonetheless important to understand the potential impact of such new definitions on the European research & development landscape.

Study methodology – An analysis of the proposed definitions of UMN and HUMN in the context of centrally approved new active substances in the last four years

The proposed definitions of UMN and HUMN pose several challenges for innovation, drug development and the regulatory process for new medicines. While some criteria (such as the absence of treatments) are unambiguous and clear on the conditions for their fulfilment, other criteria are inherently ambiguous, and their assessment is more complex and difficult to predict. This will increase the uncertainty for medicine developers and therefore limit their value as an incentive in directing innovation and impact.

In order to better understand the potential impact of the proposed definitions for UMN as well as HUMN, a cohort of 169 centrally approved new active substances between 2019 and 2022 have been assessed with regard to their ability of fulfil the proposed criteria. The analysis was based on CHMP assessments found in relevant sections from European public assessment reports.

The majority of the products from the cohort relate to a 'life threatening or severely debilitating disease'

The proposed criterion related to the disease severity (*'life threatening or severely debilitating disease'*) could be interpreted as less vague and provides a certain level of predictability for medicine developers (See Box 1). When applying this first criterion to the 111 centrally approved new active substances from the last four years (2019-2022), not being an orphan medicine (which will fall under the HUMN definition of the revised Regulation, see Box 2), the majority relate to diseases that can be considered life threatening or severely debilitating, of which many relate to various cancer indications, autoimmune diseases and severe genetic disorders (Figure 1). For 21 (18.9%) of the new active substances, the disease could not clearly be identified as a life threatening or severely debilitating disease, such as insomnia and uterine fibrosis, although these diseases can have a serious impact on quality of life.

Determining whether or not a 'disease is associated with a remaining high morbidity or mortality' can result in ambiguous outcomes

Similarly, the criterion of availability of an authorised medicinal product for the condition is also clearly identifiable. Of the 90 new active substances considered to address a *life-threatening or severely debilitating disease*, 10 (11.1%) products address a condition for which no other medicinal product is authorised in the EU, whereas 80 new active substances are indicated for a condition for which at least one medicinal product has already been authorised in the EU. However, the second part of this criterion - if a medicinal product is already authorised for the disease - relates to the disease being *'associated with a remaining high morbidity or mortality'*. This presents more challenges for the assessment as it involves an estimation of when one can speak of a 'high' morbidity or mortality. Therefore, it remains difficult to predict how this criterion will be applied in practice as well as how this will play out in different disease areas. Nonetheless, an analysis of the Committee for Medicinal Products for Human Use (CHMP) public assessment reports' description of the condition can provide at least some insights.

Of the 80 approved new active substances indicated for diseases for which a medicinal product had already been authorised, in about 60% (49 products) of the cases, the disease could be considered to be associated *'with a remaining high morbidity or mortality'* based on the description of the condition in public assessment reports. For example, because the disease is still associated with poor prognosis or, despite available treatments, still has a substantial impact on patient lives. Often CHMP refers to a UMN in these conditions. In some cases, CHMP emphasises the UMN in these conditions with the use of adjectives such as *'clear'*, *'substantial'*, *'significant'*, *'critical'* or *'high'*. The fulfilment of this criterion might be feasible, although it remains unclear how the criteria in the proposed legislation will be applied in real-world practice.

Cases also exist where the CHMP has explicitly stated that it does not consider a UMN for certain indications, such as diabetes type 2. This could indicate that products approved for diabetes type 2 will have challenges to fulfil this criterion, as this indication will not likely be regarded a disease *'associated with a remaining high morbidity or mortality'*. Diabetes is considered a major global health concern, especially for patients in which the condition remains poorly controlled, highlighting the need for new and improved treatments. If this criterion will be applied too strictly and products are therefore unlikely to satisfy the UMN definition proposed by the EC, this could impede much-needed innovation in an area such as diabetes.

Challenges arise when determining the fulfilment of the criterium relating to a 'meaningful reduction in disease morbidity or mortality for the relevant patient population'

The most challenging criterion of the Commission's proposed UMN definition (which also applies for the HUMN definition) is however the criterion whereby applicants need to demonstrate a *'meaningful reduction in disease morbidity or mortality for the relevant patient population'*. The underlying value judgments to decide whether this criterion is fulfilled make it especially challenging to predict outcomes in the early stages of drug development. This criterion depends on a range of variables. For example, it suggests the need for comparative clinical data in conditions where a medicinal product has already been approved. While this may be feasible for certain conditions, e.g., where standard treatments have been on the market for many years and can be included in clinical trials, this can be more challenging for other conditions, such as cardiovascular diseases. Only one of seven new active substances that gained a centralised authorisation with an indication for cardiovascular disease in the last four years had an active comparator. Despite the recognised burden on society of cardiovascular disease and other diseases with high prevalence and the recognised need for new treatments (e.g. with a new mode of action), improving convenience for patients of existing treatments, or the treatment of risk factors of the underlying disease such as the case with cardiovascular disease, it is challenging to demonstrate clinical benefits that translate into a 'meaningful reduction in disease morbidity or mortality' in order to satisfy the definition of UMN.

In contrast, in oncology, the line of treatment and choice of endpoint plays an important role in assessing fulfilment of this criterion. It remains difficult to predict how this criterion will be interpreted with regard to outcome measures in oncology trials (e.g., progression free survival or overall survival) as well as the implications of new treatments intended as last line treatments when patients have run out of options. Moreover, it is unclear how new treatments can sufficiently demonstrate a *'meaningful reduction in disease morbidity or mortality'* if no comparator can be used due to other reasons, for example if a treatment has only recently been authorised.

Of the 10 new active substances for life-threatening or severely debilitating disease for which no other medicinal product has been authorised for the condition, all showed a clinically meaningful benefit, such as a survival benefit in oncology indications, or an improvement on clinically relevant endpoints (Figure 1). While in a very few cases the benefit was described by the CHMP to such an extent that it can be likely considered to fulfil the criterion of demonstrating a *'meaningful reduction in disease morbidity or mortality'* (e.g. *"impressive"* or *"outstanding"* clinical benefits), it remains unclear what the cut-off values are to decide fulfilment of this criterion for all other treatments.

This becomes even more difficult for treatments for conditions for which a medicinal product has already been authorised or where there remains

uncertainty at time of approval, such as in the case of conditional marketing approvals (CMA). Of the 49 products for which this is the case, less than a quarter (10 [20.4%]) were able to demonstrate a substantial benefit over an active comparator, the majority involving products for oncology indications. If the Commission's proposal is applied such as to mandate the use of an active comparator, this could pose even more challenges to fulfilling this criterion, all the more so as it remains unclear what a 'meaningful reduction' exactly constitutes.

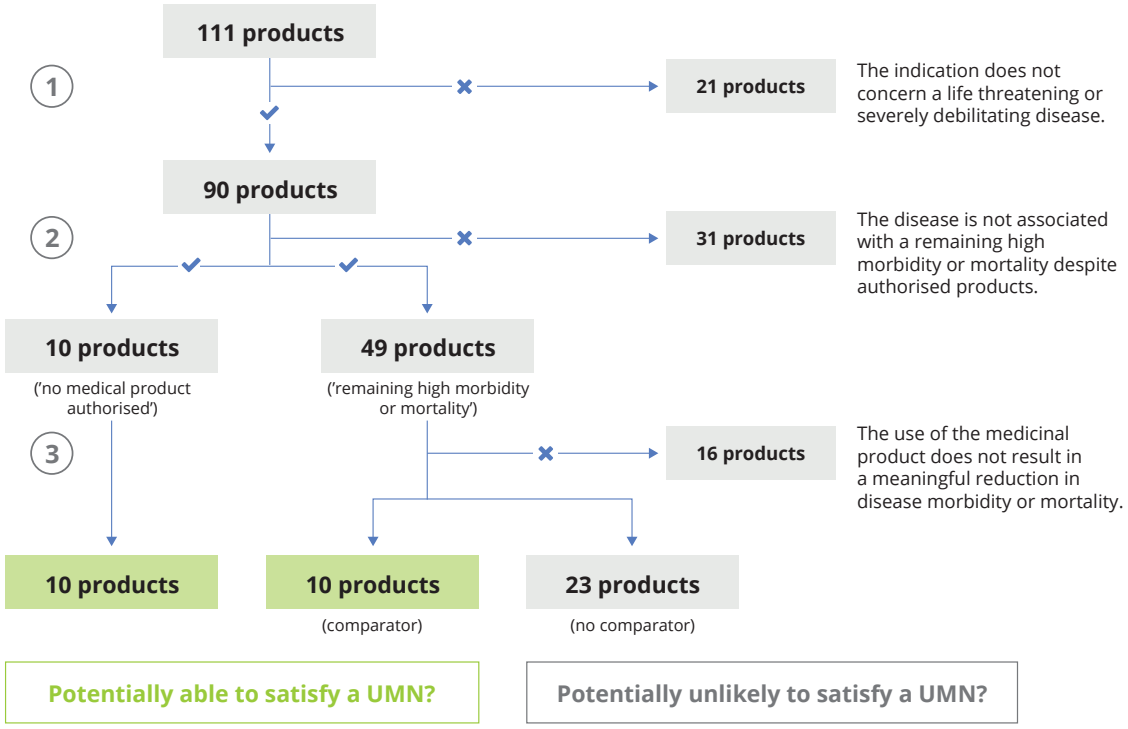

FIGURE 1.
The Commission's proposed criteria to define UMN (Directive) applied on a cohort of new active substances approved through the centralised procedure in the last four years; *(1) relating to criterion 83.1; (2) relating to criterion 83.1 (a); (3) relating to criterion 83.1 (b).*

The criterium relating to demonstrating an 'exceptional therapeutic advancement' in the proposed definition for HUMN for orphan medicines creates the largest uncertainty

The definition proposed by the EC for HUMN for orphan medicines goes even further by requiring demonstration of an 'exceptional therapeutic advancement'. This criterion creates further uncertainty as it is unclear how the EC defines 'exceptional therapeutic advancement'. It also remains to be seen if and how a common understanding of the fulfilment of this criterion can be established to create transparent and measurable outcomes and hence increase the predictability for medicine developers such as to effectively encourage investments in areas of HUMN. Another challenge is how this criterion will be applied when there exists a large amount of uncertainty at time of approval, for example, for orphan medicines with very small patient populations and inherent restrictions to demonstrate 'meaningful reduction in disease morbidity or mortality' and 'exceptional therapeutic advancement', sometimes approved through the CMA pathway or under exceptional circumstances.

Of the 58 authorised new active substances that have an orphan designation, 24 (41.4%) are indicated for conditions for which no product has been authorised yet (Figure 2). The majority demonstrated a clinically meaningful benefit according to CHMP assessment, although similar to the UMN definition, it remains unclear what clinical evidence is needed to demonstrate a *'meaningful reduction in disease morbidity or mortality'* and hence fulfilment of the HUMN definition. This becomes even more complex for orphan medicines indicated for conditions for which a medicinal product is already authorised and in addition to having a significant benefit, need to demonstrate that these products *'will bring exceptional therapeutic advancement'*. Only 10 of the 34 (29.4%) orphan medicines (for a condition for which a medicinal product is authorised) have shown a clinical benefit over a comparator, which could be considered a prerequisite by the Commission to demonstrate an 'exceptional therapeutic advancement', although unclear at this point.

The results indicate that recently approved orphan medicines have shown high clinical benefit to patients relatively often, indicating that the current orphan framework is already effective in directing innovation towards areas of highest UMN. However, the currently proposed criteria for HUMN may hamper innovation for orphan medicines by making it too uncertain to fulfil the proposed criteria, especially in conditions where orphan products are already authorised, in which case new orphan products need to demonstrate an 'exceptional therapeutic advantage'.

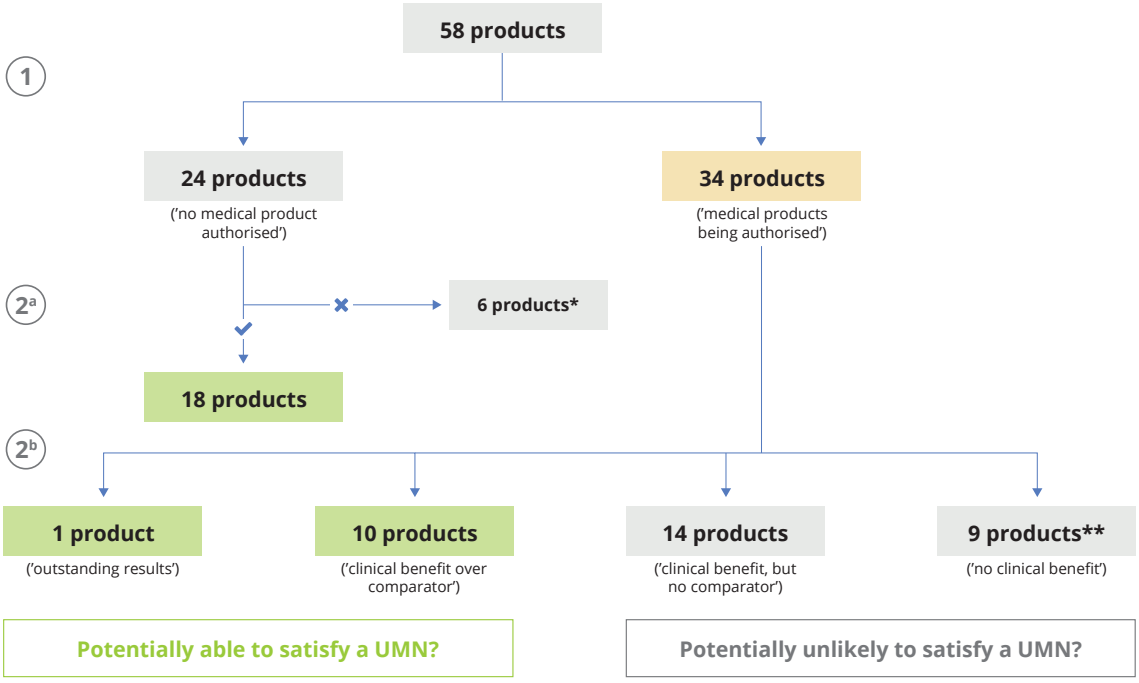

FIGURE 2.
The Commission's proposed criteria to define HUMN (Regulation) applied on a cohort of new active substances with an orphan designation approved through the centralised procedure in the last four years; *(1) relating to criterion 70.1 (a) – whether or not a product is authorised for the diseases; (2a) relating to criterion 70.1 (b) – whether the product results in a meaningful reduction in disease morbidity or mortality; (2b) relating to criterion 70.1 (a/b) relating to conditions for which a product is authorised – whether the product will bring exceptional therapeutic advancement and results in a meaningful reduction in disease morbidity or mortality;*
**products for which only a modest benefit has been shown or data considered too limited to draw firm conclusions on clinical benefit with regard to fulfilment of criterion 70.1 (b);*
***products with an observed effect that is comparable with available treatments (non-inferiority) or for which there exists too much uncertainty to draw firm conclusion about clinical benefit with regard to fulfilment of criterion 70.1 (b)*

OBSERVATIONS & CONSIDERATIONS

Generally, the concept of unmet medical need is meant to distinguish more pressing societal health needs from less pressing needs. Therefore, it plays an important role in investment and priority-setting decisions by a range of stakeholders, including regulators, HTA agencies, payers, academics and the pharmaceutical industry. Identifying a particular condition or disease area as a UMN is intended to signal its health policy significance, stimulate research activities and incentivise the development of innovative treatments, diagnoses or health technologies in these areas. Incentives associated with the identification of a UMN can take the form of preferential access to public research funds, access to alternative or accelerated regulatory pathways as well as RD incentives, consideration of UMN as a value element in HTA, and financial incentives or innovative payment models in reimbursing the health benefits a new treatment delivers.

The proposed definitions for UMN and HUMN are part of a broader framework that the Commission wants to create to provide more effective incentives for innovation that align with a number of stated objectives, including directing innovation to areas of highest need. A key challenge in the EC proposal for a definition of UMN is to achieve multiple goals through one set of criteria: it must be applicable in different therapeutic areas, transparent in its application, able to incorporate a diversity of perspectives, recognise unique and context-dependent scientific challenges and be applicable at different stages across the value chain. The proposal from the Commission provides challenges on each of these aspects, which could undermine its objectives and impact.

Applicability in different therapeutic areas: as this report shows, different therapeutic areas will raise unique challenges related to how the criteria for UMN are currently interpreted. For example, in oncology, it is unclear how the role of a new treatment for 'later' lines of treatments will be assessed or how topics such as the choice between progression free survival and overall survival as an endpoint in clinical trials will be assessed. In some therapeutic areas, such as in cardiovascular disease, treatments target risk factors for future diseases. At this moment it is unclear how the generic criteria in the legislation will apply to these and other situations.

Transparency in application: For several of the criteria, it is currently unclear how they will be applied. For example, it is unclear how a concept such as 'remaining high morbidity or mortality' will be interpreted especially in areas where medicines have already been marketed. Similarly, the term 'meaningful reduction in disease morbidity or mortality' would also need to be defined in order for any associated incentive to work and influence development decisions by innovators. Partly this lack of clarity is inherent in the fact that these are new criteria, however, it is possible to further clarify these criteria in advance, especially since there is extensive 'case history' with prior assessment by CHMP.

Incorporating a diversity of perspectives: in the proposed definition it is not always clear how different perspectives on innovation can be incorporated (e.g., policy makers, payers, patients, health care professionals etc). For example, patients and healthcare providers remain essential in helping to identify areas of UMN including conditions for which treatment options may exist. How their views, and other stakeholder views, will be included in the definition and application of criteria is as yet unclear.

Recognising unique and context-dependent challenges: In some areas with enormous scientific challenges, such as the treatment of Alzheimer's disease, it may very well be the case that new treatments will come to market in the next years, but that innovation may have an incremental nature even when new products explore innovative treatment pathways, which may prove to be important stepping stones for the future. The same could be said for various psychiatric diseases where pathology is complex, a variety of medicines is available (with limited effectiveness), yet innovative treatment paradigms are sorely needed. Discouraging such incremental innovation may have an impact on long-term innovative strength of drug development. Therefore, the criteria for defining UMN have to be adaptable to a specific disease context and incorporate context-specific challenges.

Applicability across the value chain: For an incentive framework to have an impact, it needs to provide a certain level of clarity about when criteria are achieved, in this case for UMN or HUMN. Ideally, the innovation landscape will apply the same principles across the development chain. For example, this implies that eligibility criteria for schemes such as PRIME, would need to be aligned with the UMN/HUMN criteria in the legislation and any other incentives earlier or later in the development chain (e.g. any UMN definitions used in HTA or reimbursement assessments). It was not explored to what extent this is the case.

In conclusion, while the approach by the Commission is transparent and understandable by virtue of its simplicity, challenges remain:

1. The Commission's goal to direct innovation to areas in which UMNs exist from a patient and healthcare perspective will not be addressed. In therapeutic areas that generally rely on incremental innovation to improve patient outcomes, the currently proposed criteria would likely not recognise these much-needed innovations as fulfilling a UMN, despite having a potentially significant effect on a patient's 'quality of life'.

2. Misalignment with the CHMP's current position that reflects the reality of drug development, nor does it address.

3. The application of this definition, including what constitutes a 'meaningful reduction in disease morbidity or mortality' or 'exceptional therapeutic advancement' (i.e. orphan medicines) and how this is demonstrated (e.g. long-term effects of a treatment).

Therefore, the dialogue within the EU around the definition of (H)UMN and the formulation of criteria should be informed by:

a) a multistakeholder discussion where diverse perspectives are incorporated;

b) a sound analysis of historic cases as well as assessments of products that are currently in the development pipeline to understand how such a definition will impact pharmaceutical development pipelines and selection of candidates going forward;

c) a sound analysis of which factors are also important to achieve the Commission's intent to direct innovation to areas in which UMNs exist.

This can benefit the creation of policies that are better able to achieve their intended objectives and effectively address patient needs.

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Disclaimer

This study did not assess the clinical value of individual products included in the analysis, but assessed to what extent each product might fulfil the provisional criteria to define UMN proposed by the EC. The study therefore cannot be interpreted as having any meaning for the individual products and results should not be construed as such. Since all products have received approval by the European Medicines Agency, all products have demonstrated clinical value for patients.

This assessment provides an additional overview of how UMN is currently perceived by the CHMP in the context of individual medicinal products. Although CHMP is consistent with their choice of words in assessment reports, the absence of mentioning a UMN in an assessment report does not mean that CHMP does not consider that a UMN exists. Defining UMN is a complex and multi-faceted undertaking, therefore, this analysis is meant to put the analysis of the current proposal by the EC into the broader context of how UMN is currently dealt with in CHMP assessments. This assessment is supported by Exon Consultancy (www.exon-consultancy.nl).