RSNN EXPERT MEETING - ADDRESSING THE FRAMEWORK OF UNMET MEDICAL NEED

BACKGROUND

In April 2023, the European Commission (EC) published a proposal for a new Directive and Regulation revising and replacing the existing pharmaceutical legislation. In the proposal, addressing unmet medical need (UMN) emerges a crucial aspect aimed at encouraging research and development of innovative therapies to address the UMN in several diseases.

Currently, an unmet medical need is defined as a condition for which "there exists no satisfactory method for diagnosis, prevention or treatment" or is considered a "major therapeutic advantage" over current treatments.

The proposed definition of UMN by the EC (Article 83, Directive) states that a medicinal product addresses an UMN when at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following criteria 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.

In the proposal, pharmaceutical companies are eligible for additional periods of regulatory data protection if the particular product addresses an UMN based on these criteria (+6 months). Additionally, developers of promising medicines for UMN may be eligible to receive enhanced scientific support (PRIME), accelerated assessment and conditional marketing authorisation.

The term high unmet medical need (HUMN) is being introduced for the stimulation of orphan medicinal products for rare diseases (Article 70, Regulation). Criteria to address HUMN were out of scope of this expert meeting.

EXPERT MEETING

The RSNN Expert Meeting "Addressing the framework of unmet medical need" took place on Tuesday 23 April 2024. A group of 19 experts from both private and public organisations, including regulators and HTA experts, representatives from pharmaceutical companies, researchers and practitioners from hospitals met to discuss the proposed definition of UMN from different perspectives. The expert meeting took place under the Chatham House Rule.

The discussion was guided by the following pre-defined questions:

1. What do we gain from the introduction of a definition of UMN as now proposed by the EC? Who wins, who loses?
2. Do we need a definition of UMN to stimulate the development of medicines for an unmet medical need?
3. What do we consider an UMN?
    a. What attributes may be relevant for qualifying a disease or condition as an unmet health-related need?
    b. How to identify an unmet health-related need (process, methodology, who should be involved, NEED as model?)
    c. Do we need an extra definition for high unmet medical need?
4. Are such measures compatible with the development process of new medicines? And do we believe that these measures increase access of patients to these medicines?

This report provides a summary of the experts' assessment of the EC's proposed definition of UMN.

SUMMARY

Regardless of whether one agrees or disagrees with the EC's proposal for defining UMN, there was a consensus that there is political, ethical, moral, and medical justification for narrowing the gap between regulatory processes and health technology assessment (HTA)/payer decision-making. This disparity serves as one of the driving forces behind the unequal access to new medicines across the European Union (EU). The experts expressed support for guiding drug development through incentives, drawing parallels with past practices such as current orphan drug regulations). The experts agreed that this could be achieved through a refined definition for UMN. It was evident that the ultimate goals are market availability, accessibility, and affordability. So, any mechanisms and regulatory incentives, including regulatory data protection, for industry and academia are only meaningful if these final goals are attained. These regulatory incentives should also be considered in the international context where the EU market is only a small proportion in relation to the Unites States market.

The discussion highlighted that the definition of UMN will be used throughout the whole research and development chain (from basic research to market access).
When determining a *meaningful reduction* in disease morbidity or mortality of the medicinal product for the relevant patient population at the time of market authorisation, there may be too little understanding of, for example, disease mechanisms and relevant surrogate and patient-relevant endpoints that indicate morbidity, especially in the case of rare diseases. Clarity is recommended if this should be: *likely to give a meaningful reduction* in disease morbidity or mortality. Also, it has to be clear what type of evidence would be needed at the time of marketing authorisation for the justification of the UMN. It should also be clear how to collect the data and analyse these. In addition, it should be clearly stated that when the medicinal product turns out not to give this meaningful reduction over time, whether it is possible to explore potential mitigation actions. It was emphasized that in the early stages of drug development, it was considered even harder to determine (*likely to give) a meaningful reduction* in disease morbidity or mortality of the medicinal product. In addition, if adherence to the definition of UMN will be used as an entry criterion for PRIME, accelerated assessment and conditional marketing authorisation, the definition should also be already supported by HTA/payers.
Lastly, the criterion *meaningful reduction of disease morbidity or mortality* may not always take into account patient reported outcomes like 'stabilisation', 'trend change of disease course', or Quality of Life (QoL). Also, UMN status in the context of preventive therapies with expected long-term effects will be challengingly to proof in terms of implementation and execution.

The experts preferred a high-level definition of UMN which gives guidance and allows for further specification, i.e. through EMA guidelines. It was emphasized that a high-level definition could incentivise drug development in some disease areas and, in this way, keep room for future innovations. It was not considered sensible to narrow the definition too much because as such a definition may not accommodate future innovations, small groups and new reimbursement models.

It was questioned by the experts if the current proposal will incentivise drug development for UMN. For each specific UMN it is relevant to know in which part of the research and development chain lies the limitation, and what are these limitations? The current EC proposal regarding UMN is not expected to steer or stimulate investments into drug development of more need/demand-based therapies. The proposal does not include other factors (including lack of knowledge base, disease aetiology complexity) associated with therapeutic gaps. In addition, the hurdles for reimbursement and diversity of access schemes at the national level are not addressed as well.

The experts also discussed the framework of the NEED initiative (*Needs Examination, Evaluation, and Dissemination)* as a tool to pre-identify UMN. The NEED initiative developed a framework with criteria and methods to assess the UMN of patients and society for a given health problem.[1] The experts acknowledged that this framework could serve as a starting point to assess if there is European-wide capability to identify which disease areas need action. Given that scientific knowledge is the drive for drug development, a list based on the NEED framework could be of interest to give direction in research to academic research groups via grants as well as to define avenues to establish sustainable collaborations with the industry or public-private partnerships.

In summary, the current EC's proposals regarding UMN may not be fit for purpose for future therapies. The reasons for this shortfall are twofold: conceptual, as the proposed definition is disease-a specific, while operationalisation requires substantial disease-specific knowledge (that may sometimes be incomplete/lacking); and operational, as it proves to be challenging to produce evidence justifying UMN status and lack of expected future benefits.

[1] Noordhout CMD, Levy M, Claerman R, Jaeger MD, Pauw RD, Kohn L, et al. NEED: evaluatie van onvervulde gezondheidsgerelateerde behoeften van patiënten en samenleving.