23. Unmet Medical Need

François Noël, September 2021
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In **drug discovery and development** projects, one of the classic strategies is to focus on areas of high unmet medical need (Vennemann et al., 2019). Although seemingly self-explanatory, this term must be defined in an objective and pragmatic manner, since classifying a drug as addressing an unmet medical need may confer marketing advantages and even regulatory benefits for the pharmaceutical industry.

From a regulatory perspective, an unmet medical need is defined as "*a condition whose treatment or diagnosis is not addressed adequately by available therapy*" (FDA, 2014; EMA, 2006). The FDA provides additional clarification by indicating that the term includes either an immediate need affecting a **defined population** (to treat a **serious** condition with no or very limited treatment options) or a **long-term societal need**, such as antibacterial drug resistance (FDA, 2014). Even so, objective, particularly quantitative, criteria to delimit what constitutes an "adequate" treatment are lacking. Despite this limitation, the term is widely used, both formally and informally, by different stakeholders in the health sector, including the pharmaceutical industry (both at the early planning stage of drug discovery projects and in portfolio evaluation), regulatory agencies, and public and private health organizations, often without clarity regarding the definition being applied (Vennemann et al., 2019).

In an attempt to identify a common definition and to explore stakeholder perceptions, Vreman et al. (2019) reported 16 different definitions of the term "unmet medical need". Based on their review, the authors suggest that the following three elements should be considered when defining (and "classifying") an unmet medical need: (1) availability of alternative treatments; (2) disease severity; and (3) the population affected by the disease.

The greatest challenge appears to lie in quantifying and operationalizing this concept within the broader value frameworks adopted by different stakeholders, depending on their field of activity (Vreman et al., 2019). A similar lack of consensus is observed in the scientific literature, for example in oncology, where there are calls for standardization of this terminology (Lu et al., 2017).

In a more pragmatic approach, Scavone et al. (2019) present a number of diseases that may, contextually and situationally, exhibit unmet needs, classified by therapeutic area. Examples cited by the authors include asthma, chronic obstructive pulmonary disease, diabetic retinopathy, multidrug resistance, tuberculosis, osteoporosis, Alzheimer's disease, and Parkinson's disease.

This terminological discussion is relevant because addressing an unmet medical need has become a key criterion for eligibility for preferential access to public funding,

financial incentives at the reimbursement stage, or regulatory advantages (Zhang et al., 2021). In the case of the FDA, four "expedited programs" aim to facilitate and accelerate the development and review of new drugs intended to address an unmet medical need in the treatment of a serious condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (FDA, 2014).

In Brazil, RDC 204/2017 establishes an expedited regulatory review process (up to 120 days) for the registration of medicines classified as priority, belonging to one of six categories defined in Article 3 of the regulation, without explicit mention of the term "unmet medical need":

(a) medicines used for neglected, emerging, or re-emerging diseases, for public health emergencies, or for serious debilitating conditions, in situations where no therapeutic alternative is available or when a significant improvement in safety, efficacy, or treatment adherence is demonstrated;

(b) new medicines, new pharmaceutical formulations, new therapeutic indications, or new strengths intended for the pediatric population;

(c) vaccines or hyperimmune sera to be incorporated into the National Immunization Program of the Ministry of Health;

(d) innovative or new medicines whose active pharmaceutical ingredient is manufactured in Brazil;

(e) the first three (3) applications for an unprecedented generic medicine for each active pharmaceutical ingredient or combination and pharmaceutical form, submitted by distinct economic groups;

(f) medicines included in the list of strategic products within the Unified Health System (SUS) that are the subject of a Productive Development Partnership (PDP), upon complete initial submission of all documents and studies required by current regulations.

Within the planning of a new drug discovery and development project, it is also necessary to consider the more recent concept of "future unmet medical need" that is, the unmet medical need at the time the new product reaches the market (Vennemann et al., 2019). Indeed, between the initial strategic decision to launch a new drug development project and its market entry, the standard of care may evolve, for example due to the approval of a competing product for the same disease. Thus, both the existence of a future unmet medical need and the extent to which it may be addressed by the new product significantly influence its value for patients as well as for the pharmaceutical company involved.

Finally, it is important to emphasize the distinction between the concepts of unmet medical need and essentiality. The concept of essentiality, which guided the establishment of the WHO Model List of Essential Medicines in 1977, is a useful tool for national health policy managers (Laing et al., 2003). According to the original WHO definition, **essential medicines** cover different levels of complexity and are described as "*of utmost importance, basic, indispensable and necessary for the health and needs of the population*" for which criteria of safety, quality, efficacy, and overall cost are defined

(Laing et al., 2003). This WHO list influences and guides national lists developed according to each country's characteristics. Brazil has maintained, since 1964, a list of so-called essential medicines (the National List of Essential Medicines - RENAME). Over time, this list has moved away from the essentiality criterion and has become primarily a reimbursement list for the Unified Health System (SUS) (Osorio-de-Castro et al., 2017). On the other hand, since identifying a specific medical need as "unmet" aims to incentivize innovation in that area, it is reasonable to argue that governments and regulatory agencies should recognize essentiality as a key property of unmet medical needs.

References

Laing R, Waning B, Gray A, Ford N, ´t Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. *Lancet* 361(9370):1723-1729, 2003.

Lu E, Shatzel J, Shin F, Prasad V. What constitutes an "unmet medical need" in oncology? An empirical evaluation of author usage in the biomedical literature. *Semin. Oncol.* 44(1):8-12, 2017.

Osorio-de-Castro CGS, Azeredo TB, Pepe VLE, Lopes LC, Yamauti S, Godman B et al. Policy change and the National Essential Medicines List development process in Brazil between 2000 and 2014: has the Essential Medicine concept been abandoned? *Basic Clin. Pharmacol. Toxicol.* 1:1-11, 2017.

Scavone C, di Mauro G, Mascolo A, Berrino L, Rossi F, Capuano A. The New Paradigms in Clinical Research: From Early Access Programs to the Novel Therapeutic approaches for Unmet Medical Needs. *Front. Pharmacol.* 10:111, 2019.

Vennemann M, Ruland V, Kruse JP, Harloff C, Trübel H, Gielen-Haertwig H. Future unmet medical need as a guiding principle for pharmaceutical R&D. *Drug Discov. Today* 24(9):1924-1929, 2019.

Vreman RA, Heikkinen I, Schuurman A, Sapede C, Garcia JL, Hedberg N, et al. Unmet Medical Need: An Introduction to Definitions and Stakeholder perceptions. *Value Health* 22(11):1275-1282, 2019.

Zhang K, Kumar G, Skedgel C. Towards a new understanding of the unmet medical need. *Appl. Health Econ. Health Policy*, 2021.