EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 11/47

Unmet Medical Needs

STAMP
29 January 2021

Subject: **UNMET MEDICAL NEED** - Revision of the orphan and paediatric medicines legislation

1. Introduction

Unmet medical need (UMN) is a commonly used term to describe therapeutic areas that require additional attention, where current therapeutic offerings are not yet available or not satisfactory. This term is sometimes linked to regulatory concepts, assessment of medicines or public intervention to re-direct investments in neglected areas. However, there is no universal definition of UMN, allowing different interpretations by the various constituents (patients, industry, regulators, HTA bodies and payers), depending on the context.

The recently adopted Pharmaceutical Strategy for Europe highlights the need for a common denominator and an agreed principles-based approach at EU level for UMN.

The present document aims at continuing the discussion on UMN in the specific framework of orphan and paediatric medicines. It should also inform the broader discussion as part of the Pharmaceutical Strategy. The discussion on UMN does not put in question the need for the development of therapeutic solutions for all rare diseases and for children but it aims to develop criteria for regulatory purposes and link them with tools, especially tailored incentives, to further boost development of treatments in areas where the needs are highest and to facilitate patient access to them. On 11 December 2020, the Pharmaceutical Committee concluded that further discussions are needed on how to define criteria to determine UMN for patients suffering from rare diseases and for children.

On 29 January 2021, we will continue this discussion and try to reach a preliminary agreement on the outline for these common criteria.

Also based on the feedback received on the inception impact assessment (IIA)[1] in the area of unmet medical needs, we would like to discuss the following two points in the STAMP meeting:

1. Do we agree on the common criteria for UMN in orphans and paediatric areas: disease severity, patient population and availability of alternative treatments used in combination?
2. Should a list of UMNs in rare and paediatric diseases be developed (to be updated on a regular basis) or can we establish common criteria only enabling developers and decision-makers to easily identify those areas?

2. CURRENT DEFINITIONS OF UMN

Current definitions of unmet medical needs can be found in: 1. The EU Orphan Regulation (Regulation (EC) No 141/2000); 2. Regulation (EC) No 726/2004 about conditional marketing authorisation; 3. EMA's priority medicines scheme 'PRIME'. The EU Paediatric Regulation provides instead criteria for the establishment of an inventory of paediatric therapeutic needs.

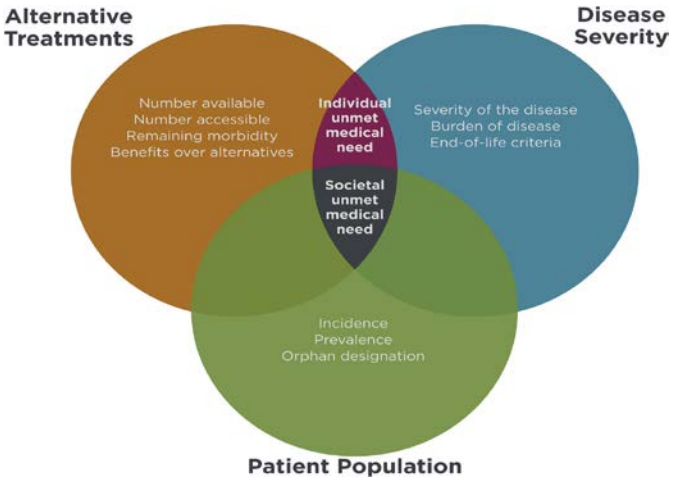

Figure 1: Common elements of unmet medical need found in definitions and possible ways to measure them[2]

- Orphan Regulation[3]

The orphan regulation does not define UMN as such but recognises the unmet need for patients suffering from rare diseases and sets criteria for designation of orphan medicines eligible for incentives:

"A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a **life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons** in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating **or serious and chronic condition** in the Community and **that without incentives it is unlikely that** the marketing of the medicinal

[1] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Revision-of-the-EU-legislation-on-medicines-for-children-and-rare-diseases

[2] VREMAN, A. ET AL., *Unmet medical need: An introduction to definitions and stakeholders perception*, Value Health (2019) (here), 1275–1282.

[3] Article 3 (1)

product in the Community **would generate sufficient return to justify the necessary investment**;

and

(b) that **there exists no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community **or**, if such method exists, that the **medicinal product will be of significant benefit** to those affected by that condition."

'Significant benefit' is defined in Article 3(2) of Regulation (EC) No 847/2000 as 'a clinically relevant advantage or a major contribution to patient care'.

- **Paediatric Regulation**[4]

"In establishing the **inventory of therapeutic needs**, account shall be taken of 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, and any data resulting from studies in third countries."

- **Regulation (EC) No 726/2004**[5]

"1. In duly justified cases, to meet **unmet medical needs of patients**, a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. In emergency situations, a marketing authorisation for such medicinal products may be granted also where comprehensive pre-clinical or pharmaceutical data have not been supplied.

2. For the purposes of this Article, **'unmet medical needs'** means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected."

3. SUMMARY OF FEEDBACK RECEIVED ON DETERMINATION OF UNMET MEDICAL NEEDS IN THE FIELD OF RARE DISEASES AND PAEDIATRIC DISEASES (INCEPTION IMPACT ASSESSMENT)

MEMBER STATES

- First step is to have a clear and common understanding as well as an unambiguous definition with transparent criteria at the EU level and to look closely at the coherence and sequence of the actions in the pharmaceutical strategy and in the orphan and paediatric regulations and incorporate this in the implementation plan of the pharmaceutical strategy.
- Clear definition and common criteria are needed at EU level for defining unmet medical needs that will be the basis for further refinement for e.g. medicines for children and rare diseases (but also for antibiotics and other disease areas). In this discussion, the

[4] Article 43 of Regulation (EC) No 1901/2006.
[5] Article 14-a.

question whether off-label use of medicines does or does not address the unmet medical need, should also be included.

- Currently, “unmet medical need” is used as a binary category (yes/no), while a quantification of the unmet need may be necessary as a basis for an award of graduated incentives.
- In principle, if a disease is considered rare, there would always be an unmet medical need.
- There is probably little discussion on the unmet need in areas where no treatment at all exist. More challenging is to determine how much the additional benefit/added-value should be of a new treatment in a domain where a treatment exists to consider it as responding to an unmet medical need.
- It is important to identify the root causes of unmet medical needs and determine whether for example the scientific knowledge of the disease is lacking or that the market is unattractive. Different root causes will need different solutions.

ACADEMIA

- It is key to get a multi-stakeholder endorsed definition of ‘unmet medical need’ to avoid a too strict definition, which may lead to a disincentivisation of drug development. Updating the list of “Therapeutic Needs” issued by the PDCO to identify unmet age-specific therapeutic needs.
- The current legal provisions of the "priority list" and the "pediatric inventory" should be translated into a global development strategy by the EMA with the participation of parents' associations.

NGOS/PATIENTS

- Unmet needs are implicit in the ‘significant benefit’ criteria for designation. An explanation to give a shared definition of satisfactory method is expected. The relevant scientifc committee, i.e. the COMP, could convene ad hoc or permanent Scientific Advisory Groups (SAGs) to address issues at hand, with a multi-stakeholder composition.
- A legally binding definition could raise more problems than it would solve, leading potentially to long discussions to the detriment of the populations intended to be served. It is preferable to ensure that early dialogue takes place at a very early stage, on a specific disease, in a multi-stakeholder format including patients’ representatives, clinicians from the European Reference Networks (ERNs) on rare diseases, regulators, HTA experts and payers, as it can help to refine existing assumptions on unmet needs and satisfactory method, under appropriate guidance.

INDUSTRY

- While crucial, the absence of any treatment is not the only unmet need to consider. Disease severity, burden of illness and impact on the quality of life of patients, families and carers are also essential elements.
- A common understanding is needed that considers all these components and the views of and benefits for all relevant stakeholders. In order to define unmet medical need a multi-stakeholder involvement is needed to overcome the narrow setting of conditional marketing authorization and include scientific and societal evaluation.

4. DISCUSSION

Way forward

Medicines for rare diseases

Coming back to the two questions in the introduction, it may be difficult to establish a list of UMN for rare diseases, also in view of the large unmet medical need in this area. The feedback received on the Inception Impact Assessment seemed to be in favour of establishing common criteria rather than a legal definition.

In view of the current criteria for unmet medical needs already in place in EU legislation, the PRIME scheme and the feedback received for the Inception Impact Assessment, there is ground to further develop common criteria for unmet medical needs in the realm of rare diseases. In addition, the upcoming impact assessment study will test options with novel incentives depending if the product addresses unmet medical needs of rare disease patients.

The three common criteria (*disease burden, patient population, availability of treatments*) are already part of the system for designation of orphan medicines. However, more clarity and refinement may be needed on their understanding and importance (individually and combined) with the double purpose of stimulating and rewarding development in all areas of rare diseases, including those of the highest needs, and facilitating patient access to them.

Medicines for children

In order to identify which would be the unmet needs for children that should be addressed, we would like to discuss the following points:

1. Article 43 of the Paediatric Regulation provides criteria[6] to establish an inventory of therapeutic needs of children:
    a. Could such criteria form a solid base to identify possible unmet needs of children?
    b. Would it be possible to be more specific with such criteria?

2. Would it be doable and manageable to setup a list of paediatric unmet needs?
3. The mechanism of action of adult products could in certain instances help to address unmet needs for children, in particular in the area of oncology.

On 29 January 2021 the STAMP meeting will be dedicated to expert discussion and brainstorming on criteria for unmet needs in rare disease and children with the aim to stimulate development of orphan and paediatric medicines addressing those needs. This discussion will be extended to other stakeholders in the next meeting of STAMP and/or the Pharmaceutical Committee.

[6] "In establishing the inventory of therapeutic needs, account shall be taken of 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, and any data resulting from studies in third countries."