European Hematology Association (EHA) views on the proposed EU Pharmaceutical Revision

8 November 2023

Unmet Medical Need

Definition of Unmet Medical Need (UMN)

EHA supports an inclusive and, above all, patient-centered definition of *unmet medical need*. Having a clear and workable definition of UMN is important to stimulate innovation and create better health outcomes for patients, as well as to preclude deceptive claims. EHA is in favor of distinguishing between High Unmet Medical Need (Art. 70 2023/0131 COD) and Unmet Medical Need (Art. 83 2023/0132 COD), with the former addressing needs pertaining to orphan diseases, as foreseen by the Commission proposal.

UMN should apply to medicinal products aimed at preventing, diagnosing, and treating disease. The definition proposed by the Commission in **Article 83** is excessively limiting, as it only covers two parameters – morbidity and mortality.

EHA advocates for a definition of UMN that responds to patient needs and considers:

- **Availability of alternative treatments**, as the standard of care is often not available or inaccessible to patients;
- **Burden of illness** on the patient, in terms of physical and psychological and social health, but also the burden on society and the healthcare system**;**
- Impact on **disease severity**, progression and duration;
- Impact on the **quality of life** of the patient.

Importantly, any assessment of whether a medicinal product qualifies as addressing an UMN *cannot* overlook patient reported outcomes (PRO) and patient experience data (PED).

Guidelines for application

Pursuant to **Article 83 paragraph 3**, EMA can adopt scientific guidelines for the application of this provision. EHA supports further specification of the criteria for UMN in these guidelines, in order to create legal certainty that is pivotal to innovation. In addition, future-proof criteria for UMN will require a re-evaluation of the parameters to keep up with clinician and patient needs across Europe.

However, the consultation process set out in **Article 162 of the proposed Regulation** (2023/0131 COD) states that patients and healthcare professionals can be consulted at the Agency's discretion. EHA advocates for a mandatory, instead of optional, consultation with HCPs and patients (advocates) to further elaborate (for instance, add quantitative requirements) and eventually revise the UMN parameters if

required. We strongly recommend monitoring the impact of UMN criteria on innovation and on patient access, in order to prevent misuse. This consultation should encompass HCPs and patients from across the EU, in order to account for regional differences. Patient and HCP involvement should be made explicit in Article 83 paragraph 3:

Article 83, paragraph 3 Directive 2023/0132 COD

European Commission proposal	EHA amendment
Where the Agency adopts scientific guidelines for the application of this Article it shall consult the Commission and the authorities or bodies referred to in Article 162 of [revised Regulation (EC) No 726/2004].	**The Agency shall adopt** scientific guidelines for the application of this Article, **further specifying the parameters for a medicinal product to address an unmet medical need. The guidelines should be precise, in order to create legal certainty, and be updated whenever required by evolving clinical and/or patient needs and in response to impact monitoring. For this purpose, the Agency** shall consult the Commission and the authorities or bodies referred to in Article 162 of [revised Regulation (EC) No 726/2004] **and ensure comprehensive clinician and patient involvement and input throughout the consultation process.**

Hospital Exemption

Hospital Exemptions (HE) are a crucial element in Europe's strategy to enhance the affordability and accessibility of innovative medicines, in particular ATMPs, contributing to the sustainability and resilience of national health systems. EHA therefore welcomes the provisions in the proposed legislation aimed at the retention and strengthening of Hospital Exemptions and warns against the rewording thereof. Article 2 provides a harmonized legal framework on hospital exemption, approved by Member State competent authorities, that improve timely and equitable access for patients to safe, effective advanced therapies. This framework is essential to create certainty and do away with current discrepancies between Member States.

EHA emphasizes that HE should not be confined to cases where no medicine for that indication is approved, considering that approval does not always translate to availability and access. ATMPs often are not available due to the marketing strategies of MAHs, high prices or negative reimbursement decisions. The taking place of clinical trials, or a compassionate use program in place for a similar indication, cannot qualify as reasons for withholding hospital exemption for several reasons: there is no guarantee that the medicinal product will actually be approved, the final indication might be narrower than initially foreseen, and there is no guarantee that a patient can be included in the clinical trial in question.
In addition, EHA points out that Member State competent authorities only approve hospital exemptions that foresee a benefit for the patient, meet regulatory requirements and are not inferior to the standard of care.

Importantly, EHA calls for reserving hospital exemptions for hospitals (both public and private). For the benefit of patients and to ensure uninterrupted access to care, the duration of the hospital exemption must not be shorter than the duration of the indication on which this hospital exemption is granted (see proposed amendment below).

Furthermore, we endorse the following requirements put forward by the Commission:

- Pharmacovigilance: The requirement for hospital exemption approval holders to comply with requirements equivalent to the good manufacturing practices and traceability and pharmacovigilance requirements for ATMPs.
- Data reporting: The requirement for hospital exemption approval holders to collect and report data on the use, safety, and efficacy of ATMPs-HE to the competent authorities at least annually.
- Data repository: The establishment of a centralized repository of data on ATMPs-HE at the European Medicines Agency (EMA), which will facilitate the sharing of information and best practices between Member States.
- Transparency: An EU-wide and globally accessible registry of all sites applying ATMPs under the HE clause with their therapeutic indications would be desirable and helpful for all stakeholders, especially patients and physicians, to be better informed concerning novel potential treatment options and their outcomes.
- Implementing acts with further specifications: In order to ensure legal certainty, for the benefit of clinicians and patients, we welcome the adoption of implementing acts specifying the EU-wide details of the application for hospital exemption approval, the format for collection and reporting of data, the modalities for the exchange of knowledge between hospital exemption approval holders, and the modalities for preparation and use of ATMPs-HE on a non-routine basis.

Article 2, paragraph 2 Directive 2023/0132 COD

European Commission proposal	EHA amendment
The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes, to the Agency.	The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes, to the Agency.
The application for a hospital exemption approval shall be submitted to the competent authority of the Member State where the hospital is located.	The application for a hospital exemption approval shall be submitted to the competent authority of the Member State where the hospital is located. **The duration of the hospital exemption approval shall not be shorter than the foreseen treatment duration, in order not to interrupt patient care. Once marketing authorization has been granted, the approval shall end.**

Article 2, paragraph 6 Directive 2023/0132 COD

European Commission proposal	EHA amendment
The competent authority of the Member State shall transmit the data related to the use, safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of that data.	The competent authority of the Member State shall transmit the data related to the use, safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of that data. **The Agency shall ensure that an overview of approved advanced therapy medicinal products prepared under hospital exemption is publicly available.**

Transparency requirements

Public disclosure of public financial support

EHA supports enhanced transparency in pharmaceutical research and development and underlines its importance for better regulation on incentives and for Member State price negotiations. Increased transparency is a crucial step towards fair pricing and affordability of medicines and, as the Commission stated in its Pharmaceutical Strategy, access for patients. However, the wording proposed by the Commission in **Article 57** provides insufficient insight into R&D costs. For that reason, EHA proposes that the provision be amended in order to include **indirect public funding**, such as tax breaks, and financial support by **charities**.

Article 57, paragraph 1 Directive 2023/0132 COD

European Commission proposal	EHA amendment
The marketing authorisation holder shall declare to the public any direct financial support received from any public authority or publicly funded body, in relation to any activities for the research and development of the medicinal product covered by a national or a centralised marketing authorisation, irrespective of the legal entity that received that support.	The marketing authorisation holder shall declare to the public any direct **and indirect financial** support**, such as fiscal benefits,** received from any public authority or publicly funded body **or charity**, in relation to any activities for the research and development of the medicinal product covered by a national or a centralised marketing authorisation, irrespective of the legal entity that received that support.

Declaration of interests

EHA supports the requirement in **Article 208 paragraph 1** for regulators and experts involved in the authorization and surveillance of medicinal products to declare their financial interests annually. This will help ensure that regulators and experts are impartial and that their decisions are not influenced by any financial interests. However, the purpose of declaration of interests should be to enhance transparency, not to exclude experts whose involvement is essential to ensure the quality and relevance of regulatory processes including scientific advice, safety and efficacy evaluations and clinical effectiveness assessments. Conflict of interest, therefore, needs to be managed rather than prohibited, especially in rare diseases with often only a small number of experts across Europe.

Regulatory processes

EHA supports the requirement in **Article 208 paragraph 2** for regulatory authorities to make their rules of procedure and those of their committees, agendas for their meetings, and records of their meetings publicly available. Importantly, meeting records should provide sufficient insight into the substance discussed. This will help ensure that the regulatory process is transparent and that the public can trust that decisions are being made in a fair and impartial manner.

Drug repurposing

EHA strongly supports drug repurposing and considers it a valuable tool for improving access and affordability of medicines for patients throughout Europe. Drug repurposing is a valuable strategy to improve patient care that can help:

- Accelerate the development of new treatments for hematological disorders. Drug repurposing can reduce the length of drug development by leveraging attested knowledge (i.e., preclinical, pharmacokinetic, and safety data) about existing drugs[i]. This is especially important for hematological disorders, which are often rare and have limited treatment options.
- Improve access to affordable treatments. Repurposing drugs is less expensive than developing drugs from scratch and submitting them for approval. Moreover, repurposing increases the availability of scientifically validated treatment options.

Whilst EHA recognizes the potential of drug repurposing to address UMN, the scope of **Article 48** should be extended to all medicinal products, as drug repurposing can address many other unsolved problems in medical care. Moreover, the "substantive evidence" prerequisite in **Article 48** requires more clarity. EHA pleads for the harmonization and simplification of regulatory procedures related to repurposing.

Article 48, paragraph 1 2023/0131 COD

European Commission proposal	EHA amendment
An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication **that is expected to fulfil an unmet medical need.**	An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication.
The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication **that concerns an unmet medical need.**	The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication.
The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.	The opinion of the Agency shall be made publicly available, and the competent authorities of the Member States shall be informed.

Market exclusivity and incentives

EHA welcomes the proposed reduction of the baseline regulatory protection and supports making additional regulatory protection conditional on the fulfilment of requirements increasing the availability of innovative therapies for patients across the EU[ii].

Whilst EHA strongly agrees with the Commission's aim to improve access to medicines across Europe, embedded in Article 81(2)(a) and Article 82 of the proposal, EHA is concerned that the foreseen requirement to release and continuously supply a medicinal product in all Member States could place SMEs at a competitive disadvantage *vis-à-vis* large pharmaceutical companies, as releasing their products across the whole EU within three years of receiving marketing authorization may still be unrealistic for some.

Finally, The European Hematology Association calls for the European Union to implement additional regulatory incentives to encourage pharmaceutical companies to conduct research and development on European soil. The European Hematology Association believes that localized research and development is essential to addressing the unique needs of patients with blood diseases in the EU. By conducting research in the EU, pharmaceutical companies can better understand the genetic and environmental factors that contribute to blood diseases in the EU population. This information can then be used to develop more targeted and effective treatments.[3] In addition, localized research and development can help to build capacity in the EU to conduct clinical trials for new blood disease treatments. This would ensure that patients in the EU can participate in clinical trials and access the latest treatments as soon as

possible (European Parliamentary Research Service, PE 697.197, 2021). Such an incentive would be a significant step towards ensuring that EU patients have access to the latest and most innovative treatments, whilst significantly improving the EU's competitive position globally, as well as its resilience and (strategic) autonomy which constitute core priorities of the Commission.

Shortages

Shortages can have a devastating impact on patients, leaving them without access to essential treatments. Shortages also lead to increased costs for healthcare systems and create disruption in patient care. EHA therefore welcomes the provisions in the proposed regulation 2023/0131 COD that address shortages of medicinal products. EHA believes that the proposed regulation has the potential to make a significant contribution to addressing the challenges facing the hematology community. Specifically:

- EHA supports the definition of shortages in **Article 2(14)**;
- EHA supports **Article 24,** mandating market authorization holders to transfer their marketing authorization in case of an intended permanent withdrawal;
- EHA supports **Article 116,** requiring market authorization holders (MAHs) to notify authorities at least 12 months in advance of a permanent marketing cessation or at least 6 months in advance of a temporary suspension will help ensure the supply of medicines;
- EHA supports **Article 117** mandating Market Authorization Holders to draft a shortage prevention plan for any medicinal products put on the market and ensure it is updated.

[i] Anticancer Fund, 2021. Manifesto on Drug Repurposing: Increasing our options for cancer treatment in Europe. https://www.anticancerfund.org/sites/default/files/attachments/acf_manifesto_19_v6.pdf

[ii] This point has also been made in the ECL position on the proposed Directive, to be accessed here: https://www.cancer.eu/wp-content/uploads/2023-09-14-ECL-position-on-the-proposal-for-EU-Pharma-Directive.pdf