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Methodology to identify critical medicines for the “Union List of critical medicines”

1. Introduction

This document outlines the methodology, governance and matrix for identifying medicines to be included in the Union list of critical medicines. It does not describe the process of drawing up or maintaining the list.

The Union List of critical medicines identifies medicines that are critical for health systems across the EU/EEA and for which continuity of supply should always be guaranteed for European patients.

The need to secure the supply of medicines across the EU and avoid shortages has been highlighted as key in the EU Pharmaceutical Strategy for Europe and the new EU pharmaceutical legislation proposal.

Although the supply of all medicines is closely monitored so that relevant actions can be taken to guarantee their availability, medicines identified as critical for public health will receive particular attention. They will be prioritised for EU-wide policy measures to improve their security of supply, including recommendations for diversification of suppliers, stimulating production within the EU or adhering to additional regulatory requirements or obligations. Other measures could include investment incentives and procurement approaches with more substantial contractual obligations for allocation and delivery.

2. Governance

The methodology to identify critical medicines was started by the European Commission Structured Dialogue initiative in 2021¹ and finalised by the HMA/EMA Task Force on the availability of authorised medicines for human and veterinary use (HMA/EMA TF-AAM).

The working group comprises shortage and clinical experts from across the EU and received input from the Joint Action on Shortages (CHESSMEN²) Work Package 6.

The methodology was adopted in June 2023 by the HMA/EMA TF-AAM Steering Committee.

¹ https://health.ec.europa.eu/system/files/2022-10/mp_vulnerabilities_global-supply_sw_d_en.pdf

² CHESSMEN (Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network): <https://www.ja-chessmen.eu/>



The assessment work linked to the vulnerabilities of the supply chain is not assigned to HMA/EMA TF-AAM and is conducted by the European Commission's DG GROW. Therefore, the final EU list of critical medicines will have to factor in assessing the vulnerabilities of the supply chain at a later stage after the ongoing EC review is finalised.

3. High-level methodology description

Critical medicines will be selected based on a risk assessment considering their relevance to public health, the so-called medicinal product criticality².

3.1. Assessment and risk assignment of medicinal product criticality

Medicinal product criticality will be based on the following two criteria:

- The **therapeutic indication (criterion 1)** of the medicine and
- the **availability of appropriate alternatives (criterion 2)**.

For criterion 1, all authorised medicines in a Member State should be classified, irrespective of their marketing status. For criterion 2, only authorised medicines marketed in the respective Member State should be classified.

For each criterion, **3 risk levels (low, medium and high)** exist. Once a risk level has been assigned for each criterion, a risk matrix is applied to assign the medicine to either of the following categories:

- “critical medicines”
- “medicines at risk” and,
- “other medicines”.

3.1.1. Criterion 1: Therapeutic indication

For **criterion 1** (therapeutic indication), the importance of the therapeutic indication will be assessed.

If a product has multiple therapeutic indications, the indication with the most serious implications for patients should determine the risk level.

High risk	Indications with very serious implications for the health of individual patients or public health : medicines or classes of medicines used to treat patients with general life-threatening acute conditions, specific life-threatening acute conditions, or irreversibly progressive conditions ³
	A medicinal product should be allocated to the “high-risk” level <u>if one or more</u> of the following conditions are met: <ul style="list-style-type: none">• Indications with very serious implications for the health of individual patients or public health: medicines or classes of medicines used to treat patients with general life-threatening acute conditions, specific life-threatening acute conditions, or irreversibly progressive conditions³

² [U.M. Musazzi, et al.; International Journal of Pharmaceutics 579 \(2020\)](#)

³ For the purpose of this sub-criteria “to treat” should be interpreted as to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action, in line with the EU definition of medicinal product.

	<ul style="list-style-type: none"> The disease to be treated is potentially fatal, irreversibly progressive or, if left untreated, will pose an immediate threat, or cause severe impairment to the patient. This applies similarly to acute situations (emergencies), chronic situations or situations with potentially fatal outcomes. If the treatment is unavailable or interrupted, it will jeopardise the vital prognosis of patients in the short or medium term or represent a significant loss of opportunity for patients regarding the severity or potential evolution of the disease. The treatment must be administered <u>immediately</u> or within regular dosing intervals.⁴ The product is part of a national disease control program (e.g., vaccination campaign)⁵
Medium risk	<p>Indications with serious implications for the health of individual patients or public health</p> <p>A medicinal product should be allocated to the medium-risk level <u>if one or more</u> of the following conditions are met:</p> <ul style="list-style-type: none"> Medicines indicated for treatment of chronic, severely limiting diseases. Medicines for the treatment of vulnerable patient groups (such as paediatric medicines). Medicines for the treatment of patient groups or diseases where a switch in medication is associated with particular difficulties. Medicines indicated for prevention or treatment of notifiable diseases. If the disease is left untreated, it may induce potentially irreversible disease progression, hospitalisation or intensified treatment, but no fatality is expected. A product which prevents relapses of a condition, but, if suspended, would not immediately expose relapses; maybe the relapse will only occur weeks or months after treatment interruption (e.g. multiple sclerosis), or the disease progression is slow (Duchenne muscular dystrophy or cystic fibrosis).
Low risk	<p>Other indications.</p> <ul style="list-style-type: none"> A medicinal product should be allocated to the low-risk level if it does not fulfil the above-mentioned high- or medium-risk conditions.

3.1.2. Criterion 2: Availability of appropriate alternatives

This risk classification aims to estimate if a potential shortage can be managed with **appropriate alternatives**, i.e. medicines that can be substituted without any negative impact on the patient's health by providing the same quality of care standard.

⁴ This requirement originates from the recommendations of the Jour Fixe on Delivery and Supply shortages. The opinion of the WS2 was, that the requirement is appropriately defined without a specific time limit. However, if during the risk assessment for medicines, the need to define a specific time period is identified, it should be defined, but should not exceed 24 hours.

⁵ The "national disease control programme" does not refer to lists of essential or critical medicines established by the WHO or available at national level.

An alternative is appropriate if it fulfils the following criteria:

- The alternative medicine is authorised for the same therapeutic indication in the respective Member State (i.e. no off-label use);
- The alternative medicine is available on the market of the respective Member State;
- Alternative treatment is clinically possible;
- The use of alternative treatment does not have a negative impact on the patient's health and provides the same quality of care standard.

Appropriate alternatives should be identified in line with the clinical considerations stated below in the table (please refer to explanatory notes).

The medicinal product will be allocated to the respective risk level based on the number of identified appropriate alternatives.

High risk	<p>Quantitative risk-classification:</p> <p><u>No</u> appropriate alternative is available;</p> <p>OR</p> <p><u>Only one</u> appropriate alternative (product) on ATC level 4 or 5 (same active substance or alternative is within the same ATC level 4 group or in another ATC level 4 group) is available -----</p> <p>Qualitative risk classification:</p> <p><i>(Clinical considerations and explanatory notes)</i></p> <p><u>High-risk treatments are those treatments for which no appropriate alternative treatment exists or is available, or switching to the alternative treatment would require extensive clinical consultations not applicable for specific indications. Substitution of treatment is expected to affect patient safety or disease prognosis.</u></p> <p>Alternative treatment is not clinically possible:</p> <p>The active substance or combination of active substances (e.g., combination of ethambutol, rifampicin and isoniazid used to treat tuberculosis, combination treatment for HIV) has unique pharmacology and no alternative treatment options exist.</p> <p>Alternative treatment would require extensive clinical consultations, not applicable for high-risk indications:</p> <ul style="list-style-type: none">• The alternative treatment has a lower therapeutic index than the initial treatment.• Switching to alternative treatment cannot be accomplished in a short time due to clinical reasons related to poor clinical outcomes, therapeutic failures, delayed onset of treatment, compromised disease control (e.g., psychiatric drugs), decreased efficacy (i. e., antibiotic resistance) or requires additional monitoring (e.g., renal or hepatic parameters).• Switching to an alternative treatment cannot be accomplished in a short time due to the organisation of care (e.g., to receive the alternative treatment, the patient may require an appointment with a different specialist who can prescribe the alternative treatment), or requires switching from self-administration to in-patient / hospital administration (e.g. switch from subcutaneous to intravenous administration).
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	<ul style="list-style-type: none"> The alternative treatment is only available for compassionate use. The alternative treatment does not meet the clinical needs of the entire target patient population: a subgroup of patients cannot use the alternative treatment / the alternative treatment is contra-indicated (including patients with specific needs, target population commonly served by off-label use, elderly, paediatric, disabled patients, etc.). The alternative treatment has additional serious, irreversible or incurable adverse events compared to the initial treatment. Due to the use of the alternative treatment, the target patient population may experience life-threatening complications (e.g., greater toxicity). <p>Alternative treatment is not available:</p> <ul style="list-style-type: none"> Alternative treatment is possible, but the alternative treatment is not available (the alternative treatment is not marketed, or the alternative product has been withdrawn from the market).
Medium risk	<p>Quantitative risk-classification:</p> <ul style="list-style-type: none"> <u>At least two</u> appropriate alternatives (products) on ATC level 4 or 5 (same active substance or alternative is within the same ATC level 4 group) are available? <p>-----</p> <p>Qualitative risk classification:</p> <p><i>(Clinical considerations and explanatory notes)</i></p> <p><u>Medium-risk treatments are those treatments for which alternative treatment requires additional input from medical personnel but is not expected to affect patient safety or disease prognosis , or the availability of alternative treatment may be limited.</u></p> <p>Alternative treatment is clinically possible but requires input from medical personnel:</p> <ul style="list-style-type: none"> Alternative treatment has the same or equal / similar therapeutic effect and may be achieved by using alternative active substances (from the same therapeutic or ATC or pharmacological group). Alternative treatment may be achieved by using alternative pharmaceutical forms or different routes of administration or extemporaneous preparations / in-house compounding, alternative strengths, or alternative dosing regimens. Using the alternative pharmaceutical form does not require switching from self-administration to in-patient administration. <p>Alternative treatment is available in limited quantities:</p> <ul style="list-style-type: none"> The alternative product is available in limited quantities, and a potential shortage is expected due to increased demand.
Low risk	<p>Quantitative risk-classification:</p> <ul style="list-style-type: none"> <u>More than two</u> appropriate alternatives (products) are available on ATC level 4 or 5 <p>-----</p> <p>Qualitative risk classification:</p> <p><i>(Clinical considerations and explanatory notes)</i></p>

	<p><u>Low risk treatments are those treatments for which alternative treatment exists, or the availability of alternative treatment is manageable. Products can freely be substituted, and little or no input from medical personnel is required.</u></p> <p>Alternative treatment is clinically possible and requires little or no input from medical personnel:</p> <ul style="list-style-type: none"> • Alternative treatment is possible by using the same active substance, the same strength in the same pharmaceutical form or a different pharmaceutical form with the same route of administration (e.g. generic substitution, substitution of formulations) • Alternative treatment is possible using a well-established alternative active substance (e.g. OTC dispensing of pain medication). • Alternative treatment is possible and does not affect patient safety. <p>Alternative treatment is readily available, and no supply issues are expected due to increased demand.</p>
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3.1.3 Overall risk categorisation

Once a medicine has been assigned a risk level for the two criteria, criticality will be set using the risk matrix (below), and the medicine will be assigned one of the following three categories:

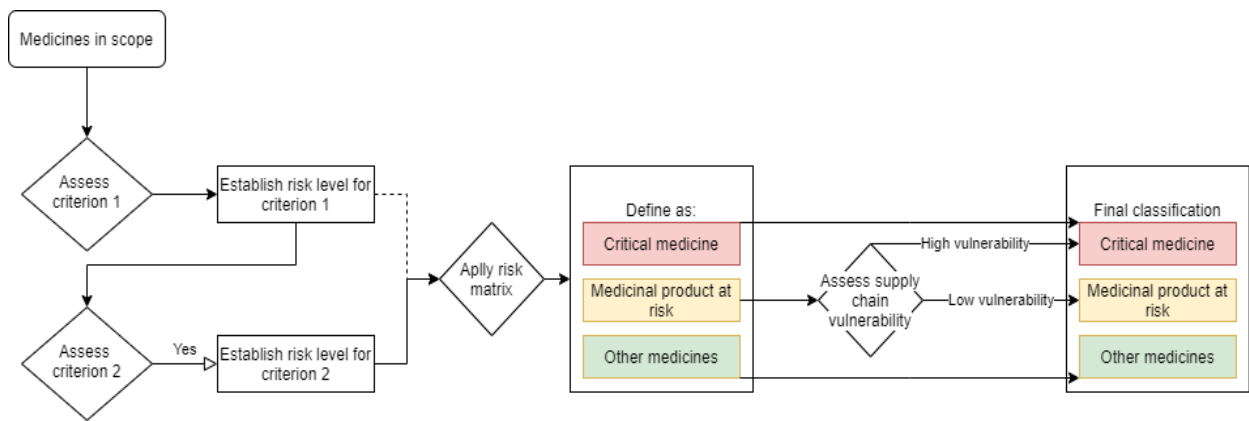
- "critical medicines"
- "medicines at risk" and,
- "other medicines".

		Criterion 1 (Therapeutic indication/ importance)		
		High risk	Medium risk	Low risk
Criterion 2 (Availability of alternatives)	High risk	Critical medicine	Critical medicine	At-risk medicine
	Medium risk	Critical medicine	At-risk medicine	Other medicines
	Low risk	At-risk medicine	Other medicines	Other medicines

3.2. Assessment of supply chain vulnerabilities

The impact of the vulnerabilities in the supply chains of the products categorised as "medium risk", the so-called "at risk medicines", also needs to be considered. The vulnerabilities in their supply chain are planned to be assessed. If vulnerabilities are identified, highly vulnerable products will be classified as "critical medicines".

The workflow diagram below illustrates the steps for the assignment of medicine into a criticality category.



The Union list will then be drafted based on the “critical medicines” assigned.