First version of the European list of critical medicines: Prescrire's comments

● A lack of transparency that the authors could swiftly rectify to allay concerns over how the list was compiled and why certain medicines are missing.

In December 2023, as part of their efforts to prevent shortages of medicines, the European Medicines Agency (EMA), the Heads of Medicines Agencies (HMA) and the European Commission published the first version of the European Union list of "*critical medicines* (...) *for which continuity of supply should always be guaranteed*" in all member states (1-3). The medicines included on this list are supposed to be prioritised in various European measures to combat medicines shortages.

This first list is intended to be expanded and updated. Its sources are the national lists of critical medicines of 6 countries: Finland, France, Germany, Portugal, Spain and Sweden (2). The French list has been widely criticised (4,5).

Two main criteria. The list was drawn up by combining 2 main criteria, each assigned a rating of high, medium or low risk. The first criterion relates to the seriousness of the medicine's authorised therapeutic indication. Indications are rated as high risk if the disease is potentially fatal (or severely disabling), if a shortage would be serious (or even fatal) for the patient in the short or medium term, if treatment must be administered within a very short timeframe, or if the medicine is part of a public health programme.

The second criterion is the number (from none to at least 3) of more or less satisfactory therapeutic alternatives on the market, i.e. the number of medicines that are sufficiently similar that substitution would have little or no impact on the patient and healthcare process (2). The situation is rated as high risk if no alternative treatment exists, or if the alternative would affect patient safety, reduce the efficacy of treatment or require additional health care (medical consultations, administration in hospital, etc.).

As a result, a life-sustaining medicine with no alternatives would be included on the list. But a life-sustaining medicine for which at least 3 appropriate alternatives are marketed, with no prospect of shortages, must not be included on the list of critical medicines (2). Details concerning the criteria for assessing the security of supply of alternative solutions are not provided in the published documents.

The document titled "Questions and answers on the Union list of critical medicines", dated 12 December 2023, states that other criteria were subsequently taken into account to determine whether a medicine would be included on the Union list, but only one is mentioned: the medicine must have critical status in at least one-third of EU/EEA member states (3).

Ratings not published. No ratings for the 2 main criteria are provided in the published list. Nor is there an appendix listing the medicines that were studied and considered non-critical. It is therefore impossible to know whether a drug's absence from the list is due to the fact that the authors of the list underestimated the seriousness of a shortage for certain patients, or considered that enough appropriate alternatives are available, or simply that they have not yet examined that particular medicine.

The EMA, HMA and European Commission would reassure many stakeholders, gain in credibility and increase the value of contributions from patients and health professionals by swiftly clarifying these points, rather than waiting for the publication of the second, updated list.

Many standard medicines missing. In the meantime, many medicines missing from the first European Union list of critical medicines raise questions about its relevance, including:

– *metformin*, the standard oral treatment for type 2 diabetes;

– *apixaban*, an anticoagulant that appears to have a slightly better harm-benefit balance than *dabigatran*, yet *dabigatran* and its antidote feature on the list, even though the clinical value of this antidote has not been established;

– angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers: no drugs of this type are listed, yet *enalapril* reduces mortality in heart failure (alternatives: *candesartan* or *valsartan*);

– *spironolactone*, a diuretic of demonstrated value in heart failure;

– *amlodipine*, one of the antihypertensive drugs shown to have long-term benefits;

– *misoprostol*, used with *mifepristone* for medical termination of pregnancy;

– oral contraceptives, especially *levonorgestrel* (the first-choice progestin for this purpose, including for postcoital contraception) and *levonorgestrel* combined with *ethinylestradiol* (the standard oestrogen for combined hormonal contraception);

– *levothyroxine*, the standard treatment for hypothyroidism;

– antivirals for the treatment of hepatitis C, yet certain combinations have demonstrated sustained efficacy in reducing viral load;

– HIV integrase inhibitors and HIV protease inhibitors, which for many patients are essential for keeping viral load at undetectable levels;

– *tenofovir* combined with *emtricitabine* for pre-exposure HIV prophylaxis;

– *nirmatrelvir* + *ritonavir*, the only antiviral treatment with demonstrated efficacy in patients at high risk of developing severe covid-19;

– pneumococcal vaccines: no such vaccines are listed, yet a pneumococcal conjugate vaccine has proven efficacy in preventing invasive pneumococcal infection in infants;
– covid-19 vaccines;
– human papillomavirus vaccines, yet they very probably reduce the risk of cervical cancer when administered before vaccinees become sexually active;
– *fluorouracil* and *capecitabine*, both first-line cytotoxic drugs, in particular for colorectal cancers;
– *docetaxel*, a cytotoxic drug that increases median survival in some prostate cancers;
– *rituximab*, a first-choice anti-CD20 immunosuppressant, for certain lymphomas in particular;
– TNF-alpha inhibitors: none are listed, despite their established clinical value in rheumatoid arthritis and Crohn's disease, in particular;
– opioid substitution treatments for opioid dependence, despite the established efficacy of *methadone* and *buprenorphine*;
– dopaminergic drugs for Parkinson's disease;
– antimalarials.

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References 1- EMA "Union list of critical medicines - version 1" 6 December 2023. https://www.ema.europa.eu/en/documents/other/union-list-critical-medicines-version-1_en.xlsx **2-** EMA "Methodology to identify critical medicines for the "Union List of critical medicines"" 29 June 2023. https://www.ema.europa.eu/en/documents/other/methodology-identify-critical-medicines-union-list-critical-medicines_en.pdf **3-** EMA "Questions and answers on the Union list of critical medicines" 12 December 2023. https://www.ema.europa.eu/en/documents/other/questions-and-answers-union-list-critical-medicines_en.pdf-0 **4-** Prescrire Editorial Staff "Liste française de médicaments essentiels: non argumentée et établie sans méthode rigoureuse" 26 June 2023. **5-** Brafman N "Médicaments essentiels: la liste du gouvernement qui fâche les médecins" Le Monde 27 June 2023.

Clinical trials: WHO draft guidance

● Prescrire has participated in a public consultation on clinical trials organised by the World Health Organization (WHO).

In September 2023, Prescrire responded to a consultation organised by the World Health Organization (WHO) concerning its draft guidance on clinical trials (1). In our response, we highlighted the positive points included in the document, as well as certain aspects that are missing from it (2).

The draft guidance points out the problem of research waste, but Prescrire would have liked to see the WHO specify who should be responsible for preventing poorly designed or underpowered trials from being launched.

Prescrire also suggested addressing other important topics in the guidance in order to help inform choices between different healthcare options. In particular, the guidance should:

– address the need to conduct comparative clinical trials versus a standard treatment of demonstrated therapeutic value, whenever such a treatment exists;
– address the weaknesses associated with the increased use of both surrogate endpoints that have not been shown scientifically to correlate with clinical outcomes, and non-comparative clinical trials: data of this kind are insufficient to generate meaningful clinical evidence;
– call on competent authorities to impose strict conditions concerning the submission of reliable evidence relating to the efficacy and adverse effects of drugs that have been granted conditional marketing authorisations: the evidence should be based on relevant clinical endpoints, and submitted within an acceptable timeframe;
– prevent manufacturers from using medical device (MD) or food supplement status for products that resemble medicinal products (as they afford lower levels of patient protection than medicinal product status), by requiring that trials show that their action is neither pharmacological, immunological nor metabolic (2).

► Translated from *Rev Prescrire* February 2024
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References 1- WHO "WHO guidance for best practices for clinical trials. Draft for public consultation" 2023: 54 pages. **2-** Prescrire Editorial Staff "Feedback form for the public consultation for WHO guidance for global practices for clinical trials" 2023: 2 pages.