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On 3 April 2020, the CPME Executive Committee adopted the 'CPME Policy on Medicine Shortages' (CPME 2020/005 FINAL).

CPME Policy on Medicine Shortages

The Standing Committee of European Doctors (CPME) represents national medical associations across Europe. We are committed to contributing the medical profession's point of view to EU and European policy-making through pro-active cooperation on a wide range of health and healthcare related issues[1].

Policy Summary

For a number of reasons medicine shortages and/or interruption in the supply chain have increasingly become an issue for Member States over the last years. Medicine shortages negatively impact public health contributing to increased costs for health systems and patients[2]. Moreover, unavailability of medicines can significantly limit doctors' ability to provide appropriate treatment. Therefore, there is a need to prevent shortages, tackle those already existing and increase the transparency of the supply chain. The current crisis concerns all Member States and demands a common European response[3].

The proposed measures include communicative, organisational and legislative solutions.

They comprise monitoring of medicine shortages at the EU level and establishing tools for information exchange among Member States, adopting widely agreed definitions of medicine shortages and essential medicines, and influencing distribution of medicines by stockpiling and parallel trade.

The EU should become more independent in supplying medicines to European citizens and diversify providers in the European market. Moreover, there is also a need to enhance and enforce current obligations of the pharmaceutical industry, including a clarification of the Directive 2001/83/EC on the Community code relating to medicinal products for human use.

[1]CPME is registered in the Transparency Register with the ID number 9276943405-41.
More information about CPME's activities can be found under www.cpme.eu

[2]T. Bochenek, V. Abilova, et al., *Systemic Measures and Legislative and Organizational Frameworks Aimed at Preventing or Mitigating MedicineShortages in 28 European and Western Asian Countries*, Front. Pharmacol. 8:942., January 2018, doi: 10.3389/fphar.2017.00942

[3]A. Acosta, E. P. Vanegas, et al., *Medicine Shortages: Gaps Between Countries and Global Perspectives*, Front. Pharmacol. 10:763., July 2019, doi: 10.3389/fphar.2019.00763

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A. Shortages in the EU

Although medicine shortages are not a new phenomenon, there is a clear increase in Europe over the last years. The current crisis concerns the entire EU across all health care settings affecting supply of day-to-day and essential medicines[4]. Medicine shortages are a daily experience of doctors, and hospital and community pharmacists. Significant unavailability of medicines has been reported by most EU Member States.

A pan-European survey among hospital pharmacists has identified shortages as a major problem in the hospital sector, with an overwhelming majority of respondents stressing that shortages have become more troublesome during the last years[5]. A similar increase is reported by community pharmacists[6].

To prevent supply problems, several Member States have already undertaken actions at national level addressing the export of certain medicines, stockpiling or the reinforcement of legal obligations of pharmaceutical companies and wholesalers[7].

B. Impact of shortages on patients, doctors and health systems

Medicine shortages are a growing public health threat with a serious impact on health care systems and public health. They can severely limit doctors' ability to provide appropriate treatment.

Medicine shortages have an unquestionable impact on public health.

They contribute to increased costs for health systems (e.g. purchasing more expensive medicines, increasing inventory levels or additional workforce spending) and patients (e.g. paying for more expensive or non-refundable alternative medicines).

A medicine shortage means in practice that doctors cannot give the necessary medicines to patients. That can lead to possible delays in patients' treatment, to the need to switch to alternative therapies

[4]The Pharmaceutical Group of the European Union (PGEU), *Position Paper on Medicine Shortages*, Brussels, 2019, p.2.
[5]The European Association of Hospital Pharmacists (EAHP), *2018 Medicines Shortage Survey*, Brussels, 2019, p.6.
[6]According to a study by the Pharmaceutical Group of the European Union (PGEU) all responding countries experienced medicine shortages in community pharmacies over the previous year, and most of them indicated that the situation worsened compared to 2018. See: The Pharmaceutical Group of the European Union (PGEU), *2019 PGEU Medicine Shortages Survey*, Brussels, 2020, p. 3.
[7]Head of Medicines Agencies (HMA), *Availability of medicinal products for human use*, October 2019, see also: Heads of Medicines Agencies (HMA) / European Medicines Agency (EMA), *Good practice guidance for communication...*, EMA/632473/2018, July 2019 and HMA/EMA, *Guidance on detection and notification of shortages of medicinal products...*, EMA/674304/2018, July 2019.

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that could be less effective, to adverse effects and adherence problems or even life threat when a shortage concerns essential medicines[8].

Medicine shortages result in additional workload for doctors and pharmacists as they must spend time managing the unavailability, tracking inventory, identifying alternatives and making decisions about rationing scarce supplies.

Scarcity or unavailability of medicines can create situations in which physicians have to make a choice of providing a certain treatment to one patient while denying it to another. The decision whether to deny a treatment or to change a medication plan raises serious ethical questions as regards equality and can affect the relationship of trust between a physician and the disadvantaged patient.

C. Addressing shortages at EU level

1. Identifying root causes

Medicine shortages are a multi-factorial problem that can stem from unpredictable and predictable causes. They can result from different economic, manufacturing or regulatory reasons[9].

Currently, the majority of Active Pharmaceutical Ingredients (API) and medicines are produced outside of Europe in limited number of manufacturing sites. Distant location of factories makes it more difficult to inspect them and results in longer, less transparent and fragile supply chains[10]. Unforeseen disruptions or quality and production problems have far-reaching consequences. Moreover, at the production sites, delays in supply can also result from the shortages of raw materials[11].

Besides, the shortages can be also caused by the pharmaceutical industry's pricing strategies, products discontinuations from unprofitable markets or imposing supply quotas[12].

Other potential root causes include national tendering procedures focused solely on the price criteria, parallel trade, stockpiling on national level that can endanger situation in other Member States or increased demand.

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[8]Medicine shortages jeopardize rational pharmacotherapy and patient safety, especially if essential medicines are not available. There are several reasons of that e.g., as the medicines recommended on the basis of solid evidence in Clinical Practice Guidelines cannot be prescribed, necessary changes in treatment regimens in response to medicine shortages (e.g. psychotropic, anti-epileptic and oncology medicines) alter the efficacy and tolerability of the treatment and – of crucial importance – this often leads to medication errors.

[9]The Economist Intelligence Unit, *Addressing medicine shortages in Europe…*, The Economist Intelligence Unit Limited, 2017, pp. 10-14. For the root causes identified on the US market see also: Food and Drug Administration (FDA), *Drug Shortages: Root Causes and Potential Solutions*, 2019, pp. 21-31.

[10]R.E. Ferner, J. K. Aronson, et al., *Crisis in the supply of medicines*, BMJ 2019;367:l5841, October 2019, doi: https://doi.org/10.1136/bmj.l5841

[11]World Health Organization (WHO), Medicines shortages, WHO Drug Information Vol. 30, No. 2, 2016, pp. 180-181.

[12]M. Beck, J. Buckley, *Managing pharmaceutical shortages: an overview and classification of policy responses in Europe and the USA* SAGE journals, March 2019, https://doi.org/10.1177/0020852318815330

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As these potential causes are interlinked a comprehensive response is needed.

However, dedicated research on medicine shortages in Europe is scarce[13]. The particular root causes affecting EU Member States need to be identified and concrete solutions defined. An independent study led by the European Commission is a prerequisite to undertaking effective actions.

2. The role of EU institutions

CPME recognises various recent and current initiatives in the EU institutions[14]. However, EU action should take a more coherent approach. CPME strongly advises to establish a European action plan on access to medicines that would include the measures proposed in this policy and take into consideration solutions suggested in other papers[15].

In December 2019, the Finnish Presidency of the EU emphasised a need to take concrete measures by Member States and the European Commission to ensure medicines availability[16]. Subsequently, the Croatian EU Presidency and the German EU Presidency have committed to address pharmaceutical policy with a focus on availability of medicines.

Likewise, Member States have proposed to set up an EU agenda on pharmaceutical policy 2020-2024 with the focus on identifying the root causes of current shortages and means to tackle them[17].

The European Commission has a strong political mandate to address medicine shortages[18]. The Commissioner for Health, Stella Kyriakides, has committed to tackle the crisis and to submit a communication on pharmaceutical policy in late 2020[19].

Given supervision of medicines, input from national registries, and information from all agencies in Europe, CPME recognises EMA the body best suited to take the responsibility of the European response

[13]T. Bochenek, V. Abilova, et al., *Systemic Measures and Legislative and Organizational Frameworks…*, *Op.cit,* p.2; European Healthcare Distribution Association (GIRP), *Medicine Shortages in Europe and Their Impact on Patients*, October 2018, p.3.
[14]Council of the European Union, *Council conclusions on strengthening the balance in the pharmaceutical systems...*, 2016/C 269/06. July 2016; European Parliament, *European Parliament resolution on EU options for improving access to medicines*, P8_TA(2017)0061, March 2017.
[15]World Health Organisation (WHO), *Addressing the global shortage of, and access to, medicines and vaccines*, EB142/13, January 2018; EAHP, *EAHP Position Paper on Medicines*, Revised version adopted in June 2019; HMA/EMA, Heads of Medicines Agencies (HMA) / European Medicines Agency (EMA), *Good practice guidance for communication...*, Op. cit.; HMA/EMA, *Guidance on detection and notification…*, *Op. Cit*.
[16]Council of the European Union, *European pharmaceutical policy - strengthened cooperation and coordination with the aim to improve access to medicines*, Brussels, November 2019.
[17]Council of the European Union, *Meeting of the Employment, Social Policy, Health and Consumer Affairs Council*, December 2019.
[18]European Commission, *Mission letter to Stella Kyriakides, Commissioner for Health and Food Safety*, Brussels, 1 December 2019, p.4.
[19]Council of the European Union, *Meeting of the...*, *Op Cit*., December 2019.

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to medicine shortages. EMA published guidelines in 2019[20], created a catalogue on medicine shortages[21] and established a task force on the availability of authorised medicines for human and veterinary use, along with the Heads of Medicines Agencies (HMA)[22]. Moreover, the second phase of a pilot project of the EU Single Point of Contact network is ongoing[23].

Nevertheless, CPME observes that EMA's capacity and role in addressing medicine shortages is insufficient. EMA should be provided with a better mandate and better infrastructure. Moreover, EMA should be entirely publicly funded as a prerequisite to its independence.

D. Strengthened cooperation, centralised actions and dedicated leadership

To eliminate and prevent shortages, significant measures must be taken by all Member States and their national competent authorities coordinated by the EU.

These should refer to a package of measures targeted on communication, organisation and legislation level.

1. Steering distribution of medicines

Medicine shortages can be addressed by measures related to their distribution that include stockpiling or restricting parallel trade.

When needed, stockpiling of medicines should take place at EU level. National stockpiling should only be introduced when not endangering neighbouring countries, regions or health care facilities with patients in need of the stockpiled medication. To prevent a shortage, stockpiling for essential medicines should be introduced lasting at least four weeks in hospitals and two to three months in wholesalers' inventories.

Moreover, Member States should be allowed to temporarily ban parallel export. By parallel trade, medicines can be exported from Member States where they are relatively cheaper to the markets where their prices are higher. Temporal ban of parallel export of medicines in or at risk of shortage may help to avoid arise or aggravation of medicines' unavailability in countries at risk. Importantly,

[20]Heads of Medicines Agencies (HMA), European Medicines Agency (EMA), *Guidance on detection and notification of shortages of medicinal products for Marketing Authorization Holders (MAHs) in the Union (EEA)*, July 2019; Heads of Medicines Agencies (HMA), European Medicines Agency (EMA), *Good practice guidance for communication to the public on medicines' availability issues*, July 2019.
[21]European Medicines Agency (EMA), *Shortages catalogue*, accessible at: the EMA's website.
[22]Heads of Medicines Agencies (HMA) / European Medicines Agency (EMA), *Task force on the availability of authorised medicines for human and veterinary use*, accessible at: the HMA's webiste.
[23]European Medicines Agency (EMA), *Highlights of the EMA Management Board meeting*, December 2019.

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applying such a measure must be justified, reasonable and proportionate to ensure a legitimate public interest[24], not to infringe the principles of free trade and movement of goods within the EU[25].

While addressing the distribution of medicines in shortage, the EU and Member States should be very cautious about online sales of medicines. The safety of medicines sold online must be guaranteed. Still, too many illegal online practices can be found. Illegal online pharmacies can sell prescription medicines without medical prescriptions and professional supervision (often at a higher price), taking advantage of traditional supply disruptions.

Moreover, it should be explored whether to establish a central European database on medicines supply to the EU market which could include information on: which country authorised the medicine, under which trademark, whether it was resupplied to or withdrawn from the market and its supply status.

2. Monitoring, communication and common terminology

Communication is crucial in preventing shortages. Doctors must have access to up-to-date information to be able to adequately respond to arising and existing shortages. Early awareness of a supply problem and early identification of potential therapeutic alternatives may mitigate the possibility for adverse reactions endangering patient safety.

Moreover, it is critical to establish a standardised reporting system giving guidance as to what, when and how to report. Producers and importers should be obliged to report existing or arising shortages to the national competent authorities and the EMA. However, the reporting system will not properly function unless common definitions of a medicine shortage and clinically essential pharmaceuticals are agreed. The WHO, EMA and other stakeholders should join forces to work on a common terminology applicable at EU level and globally.

An EU-wide reporting system requires an agreed electronic template to be used. The EMA should propose such standard in consultation with the users (i.e. producers, physicians, pharmacists, hospitals etc.) and competent authorities. This could follow the example of the Commission´s IMI (Internal Market Information System) communication tool.

Information reported to the EMA should be made accessible to all competent authorities in Member States who should decide whether the information should be published or made available to the other supply chain actors (physicians, pharmacists and hospitals) in a user-friendly format.

[24]European Commission, *Infringement: Parallel trade of medicines*, Press Release, May 2018.
[25]Art 26 and Art 28-37 in: *Consolidated versions of the Treaty on European Union and the Treaty on the Functioning of the European Union*, Official Journal C 326 , 26/10/2012 P. 0001 - 0390, October, 2012, Art 26 and Art 28-37.

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E. Increasing diversification of supply sources and reducing Europe's reliance on external manufacturing

Member States should adopt policies to increase diversification of supply sources and become more independent from production sites outside Europe, most importantly in case of essential medicines.

The current overreliance on manufacturing sites located in third and remote countries for the production of active pharmaceutical ingredients and medicines constitutes a real threat to the secure and stable supply in the EU. As an example, production sites could be affected by export restrictions in the countries of production. Clearly, Europe (as all other parts of the world) need to be able to steer production depending on its own needs. Bringing the production of essential medicines back into the EU could make the supply chain more transparent and would allow for an easier and more effective monitoring of manufacturing sites.

In view of the above, the EU should explore regulatory measures or financial incentives to shift the production of essential medicines back to Europe. This however should not compromise on quality, environmental or work safety standards in Europe.

Secondly, it should be examined how to diversify supply sources to ensure a better presence of providers on the European market. Dependence on a small number of drugs' suppliers can lead to shortages in case of the shutdowns of their facilities, regardless of the reasons. The ultimate goal of all providers should be to have at least two or three manufacturing sites as they can be subject to accidents and disruptions.

Moreover, the European Commission should engage with the Member States in a structured exchange of best practices on procurement procedures for medicines, issuing recommendations. Member States should be encouraged to apply other criteria than price in national tendering procedures such as reliability of supply and the number and location of production sites. One solution could be the creation of a label "medicine made in Europe" which national health systems can use as a requirement in tendering procedures.

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F. Enhancement and enforcement of current obligations of pharmaceutical companies

1. Clarification and enforcement of the Community Code Directive

Current legislation does not ensure the stable supply of medicines. Clear regulatory guidance at EU level will help to avoid a heterogenous transposition by Member States and will enable a better response to shortages[26].

The Directive 2001/83/EC[27] (the Community Code Directive) as the centrepiece of EU pharmaceutical legislation stipulates the obligations of market authorisation holders (MAH) entering the EU market. The Community Code directive obligates MAHs– "within the limits of their responsibilities – to ensure appropriate and continued supplies of medicinal products to cover the needs of patients" (Art 81). Moreover, in case of problems with such supply, either temporal or permanent, "MAHs are obliged to notify competent authorities at least two months before the interruption of the product placing on the market" (Art 23a).

The Community Code Directive requires clarification. The "limits of their responsibilities" must be specified. In fact, do current cases of shortages violate Art 81? And if so, what are the consequences? Obviously, the Directive cannot be enforced as it doesn`t provide for sanctions. The Community Code Directive must be strengthened to hold companies accountable.

Moreover, the Community Code Directive requires the introduction of an early warning system allowing for efficient communication on medicines supply status, see D.2.

2. Public service obligation to supply essential medicines

Essential medicines are not simple items of commerce[28].

As they are a critical component of patient care, appropriate access to essential medicines and prevention of their shortage cannot be addressed by "normal" market mechanisms. Essential medicines are a public good and should be always available and accessible. Therefore, to assure their stable supply, a public service obligation (PSO) should be imposed on their providers that should fulfil their duty of care. Moreover, it should be also explored whether the use of PSO could be justified in any other situation in that a medicine shortage might pose a risk to patient health[29].

[26]European Commission, *Summary of Responses to the Questionnaire on the Measures implemented in the Member States territories in the context of Article 81 of Directive 2001/83/EC,* May 2018.
[27]Directive 2001/83/EC, *Community code relating to medicinal products for human use*, OJ L 311, 28.11.2001, p. 67, November 2001.
[28]The European Association of Hospital Pharmacists (EAHP), *Medicines shortages in European hospitals* , Brussels, 2013, p. 2.
[29]P.H. Truong, C.C. Rothe, T. Bochenek, *MedicineShortages and Their Impact on Patients and Health Care Systems…, [in:]* A. P. Barbosa-Povoa et al. (eds.), *Pharmaceutical Supply Chains—Medicines Shortages*, Springer Nature Switzerland AG 2019, p. 67, https://doi.org/10.1007/978-3-030-15398-4_3.

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Recommendations

- CPME calls on EU Member States to strengthen their collaboration and focus on common European solutions to medicine shortages.

- CPME calls on DG SANTE to better engage in addressing the problem benefiting from its strong mandate. DG SANTE should identify the root causes of the medicine shortages in the EU and establish a European action plan to tackle them.

- CPME calls on the European Commission to empower EMA by ensuring its independence and providing it with the required infrastructure and mandate.

- CPME calls on the European Parliament to address the problem in the ENVI Committee and make its own initiative report.

- CPME calls for monitoring of shortages at EU level and for the development of information sharing tools between EU Member States, including a common reporting template.

- CPME calls for the development of an agreed terminology and uniform definitions of what is a medicine shortage as well as clinically essential and non-essential pharmaceuticals that can be adopted on EU level and globally. The developed European list of essential medicines should serve as a basis for any measures against shortages at EU level.

- CPME argues that when needed, medicines' stockpiling should take place on EU level, and in case of ineffectiveness of other solutions, EU Member State should be allowed to temporarily ban parallel export.

- CPME calls on the European Commission to explore regulatory or financial incentives to shift the production of most important active pharmaceutical ingredients and medicines back to Europe and diversify supply sources on the EU market.

- CPME calls on the European Commission to propose legislation to clarify the Market Authorisation Holder's obligations under the Directive 2001/83/EC and develop an enforcement mechanism including penalties.

- CPME calls on the European Commission to encourage Member States to revise their national tendering procedures with a view to including other criteria than price, e.g. by creating a label "medicine made in Europe".

- CPME calls for considering essential medicines as a public good and for imposing a public service obligation on MAHs to assure their stable supply.

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