

European Society of Cardiology views on the EU Pharmaceutical Strategy

The Pharmaceutical Strategy and the burden of heart disease

The European Society of Cardiology (ESC) warmly welcomes the decision to launch a new EU Pharmaceutical Strategy as we believe that adequate medicines policy could significantly contribute to address the increasing burden of cardiovascular disease (CVD) (see box)ⁱ.

The ESC shares the views of the European Commission that citizens and patients across Europe should benefit from equal access to safe, state-of-the-art, innovative, and affordable medicines, and that the EU Pharmaceutical Strategy can play an important role in achieving this.

More specifically, the ESC calls on the Strategy to:

1. Adopt a common response in the EU to shortages of medicines
2. Support the adoption of the legislation on health technology assessment
3. Promote research on innovative and promising pharmaceutical therapies for heart disease
4. Prevent the misuse of the Orphan Medicinal Products Regulation

1. Adopt a common response in the EU to shortages of medicines

We are extremely concerned about medicine shortages in the EU. Shortages have been reported, amongst others, for crucial medication for acute and chronic cardiovascular disorders, including antihypertensives, diuretics, dobutamine, but also short-acting sedatives, antibiotics and other medicines used in acute cardiovascular care, cardiovascular interventions and surgery. Medicines shortages have multiple root causes including economic related issues and supply chain issues.

The burden of heart disease

Cardiovascular diseases (CVD) are the largest cause of death in the EU and worldwide. In the EU, more than 1.8 million people die every year as a result of CVD, accounting for 36% of all deaths (in comparison, cancer accounts for 26% of all deaths in the EU). Furthermore, CVD accounts for a large proportion of premature deaths (before age 65) in the EU: 24% for men and 17% for women. In the EU more than 60 million people live with CVD, and 13 million new cases of CVD occur every year. In addition, CVD is the leading cause of the overall disease chronic burden, above cancer or mental and substance use disorders, and it is projected that this will remain the case over the next 20 years. CVD is estimated to cost the EU economy €210 billion per year, and in some countries CVD costs represent more than 20% of total healthcare expenditure. COVID-19 has exacerbated this scenario, prompting CVD experts to warn about the short and long term effects of COVID-19 on cardiovascular care.

There are several initiatives that could be adopted at European level to try to prevent this situation. We believe that defining – in collaboration with academic organisations and healthcare providers – a list of essential medicines (such as the List of Essential Medicines published by WHO)ⁱⁱ and their possible alternatives, could help to focus concrete policies to ensure the supply of those medicines. Other measures

To reduce the burden of cardiovascular disease.

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include establishing an effective system to map the true burden of shortages, improved communication and coordination of supplies in Europe, and the establishment of coordinated tendering and procurement mechanisms.

- **We call on the Commission to propose measures to prevent shortages.** In particular, the Commission should facilitate the agreement of **a list of essential medicines** and adopt policies to ensure their continuous supply.

2. Support the adoption of the legislation on health technology assessment

Health technology assessment (HTA) is an important instrument to improve access to effective medical technologies, contributing to the sustainability of national healthcare systems, and delivering added value to patients. The introduction of joint HTAs at EU level would reduce the fragmentation of assessment systems, the duplication of efforts, and the misallocation of resources within the EU.

- **We call on the Commission to include joint HTA as a fundamental pillar of the Pharmaceutical Strategy.** The ESC advocates that the proposal for an EU Regulation on HTA will be agreed as soon as possible.

3. Promote research on innovative and promising pharmaceutical therapies for heart disease

Despite the high burden of heart disease, research and innovation in CVD are lagging behind developments for treating diseases of other systems. Globally, innovation in cardiovascular medicines has declined for more than a decade, in terms of new medicines coming to marketⁱⁱⁱ. This trend is confirmed by data from the USA^{iv} as well as from the European Medicines Agency.

In 2018, no new CVD medicines with a new active substance were recommended for approval by EMA^v (while 11 new cancer medicines and 21 new orphan medicines were centrally approved). In 2019, only 2 new CVD medicines with a new active substance were approved^{vi} (compared with 5 new cancer medicines and 7 orphan medicines). Moreover, since 2014 the vast majority of patents filed in the cardiovascular field originate from the USA, with the number filed by Germany, France, Italy and the UK together being only 35% of the that number^{vii}.

The causes of this decline include the high cost of clinical trials in cardiology and an unfavourable regulatory framework for fostering CVD innovation.

Due to a combination of factors, including the need to base the assessment on large populations, clinical trials in CVD are more complex, larger, longer and more expensive than those for other conditions. The average pivotal CVD clinical trial costs three times more than its cancer counterpart and six times more than trials for most other diseases.^{viii,ix}

The excessive cost of cardiovascular trials is a major threat to the development of new treatments and has led several pharmaceutical companies to lower the priority of, or even end, developing CVD medicines.^x

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To address this problem, innovative approaches are needed. These include a regulatory framework with better and more flexible rules for the conduct of clinical trials (envisaging the use of novel technologies) and better-quality patient registries in CVD, which would allow the use of real-world data and the carrying out of registry-based studies.^{xi}

The EU Clinical Trials Regulation will bring some positive changes. However, reliance within the EU on the application of the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidelines for the design and conduct of clinical trials is of concern. The overenthusiastic implementation of those guidelines has created much of a burden failing to produce the intended benefit for patients.

- **We call on the Commission and the European Medicines Agency (EMA)** to simplify the requirements for the conduct of clinical trials, and we support the revision **of the ICH E6 GCP guidelines to avoid unduly complex requirements for conducting trials.**
- **We urge the Commission** to speed progress to adopt policies **to foster the use of digital technologies.** The digitisation of health systems would allow fast recruitment of patients to participate in randomised clinical trials and the collection of outcomes from electronic health records or registries accurately. It would also allow the undertaking of safety surveillance and the testing of the efficacy and safety of medicines and devices for common diseases such as CVD at a lower cost. This would facilitate access to new treatments and bring industry investment to Europe.

Moreover, the pharmaceutical strategy should optimise the use of registries as a source of real-world evidence to support decision making^{xii}. Registries can be used to generate evidence during the evaluation of medicines. Appropriate governance procedures should be developed to safeguard transparency, accessibility of data and the independence of registries, and to provide clarity about legal and regulatory requirements.

- **We call on the Commission to facilitate the development of registries** adopting appropriate governance procedures and proposing financial incentives and sustainable funding to help scientific societies to build independent registries.
- Finally, the EU regulatory framework incentivising medicines developers should be revised to ensure that unmet medical needs are better addressed. In this regard we were glad to see that the Pharmaceutical Strategy consultation document referred to reinforcing innovation in areas of most need. **We call on the Commission to strengthen incentives** to ensure that unmet medical needs **including in high prevalence disease** areas such as CVD can be addressed.

4. Prevent the misuse of the Orphan Medicinal Products Regulation

While we support the objectives of the Orphan Medicinal Products Regulation, we are concerned by its misuse. The Regulation was recently used to gain orphan status for an "old" medicine used to treat a CVD

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condition: mexiletine. Following the award of orphan market exclusivity rights, the price of mexiletine has disproportionately increased with a damaging impact on access to the medicine by patients.

Mexiletine was developed in the late 1960's, early 1970's and is used to treat arrhythmias. Although other anti-arrhythmic medicines have now surpassed mexiletine, it is still used to treat dangerous heart rhythm disturbances when other pharmacological and /or invasive interventions fail. In addition, it is still acknowledged in both European and USA guidelines for ventricular tachycardia and ventricular fibrillation and sudden cardiac death prevention, either as monotherapy or in addition to other medicine or intervention. Moreover, there are no other alternative (outpatient) for the same indication to prevent ventricular tachycardia and ventricular fibrillation.

Since the 1980's mexiletine had been used off-label to treat non-dystrophic myotonias (muscle stiffness) and in 2014 mexiletine acquired European orphan designation to treat such disorder. In December 2018 EMA granted marketing authorisation to Namuscla (INN mexiletine) to treat Myotonic Disorders. Since January 2019 mexiletine is only delivered under Namuscla and the price of the medicines has skyrocketed. Nowadays, European health care systems are forced to accept, negotiate or deny the price rise and risk (further) problems in mexiletine availability for patients who depend on this medicine^{xiii}.

The Pharmaceutical Strategy should consider changes to the Orphan Medicinal Products Regulation to ensure that situations such as the one described above are avoided. For instance, provisions could be introduced to exclude known indications or known use of existing medicines from orphan designation eligibility.

- **We call on the Commission to amend the Orphan Medicinal Products Regulation to prevent the abuse of the legislation to the detriment of patients and health care systems.**

ⁱ European Society of Cardiology & European Heart Network. Fighting cardiovascular disease – a blueprint for EU action, 2020

ⁱⁱ WHO Model Lists of Essential Medicines, <https://www.who.int/medicines/publications/essentialmedicines/en/>

ⁱⁱⁱ Hwang T. et al. Temporal Trends and Factors Associated with Cardiovascular Drug Development, 1990 to 2012, Journal of the American College of Cardiology, Basic to Translational Science, 2016

^{iv} McClellan M. et al. Call to Action: Urgent Challenges in Cardiovascular Disease, Circulation, 2019

^v European Medicines Agency, Human medicines highlights 2018, https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2018_en.pdf

^{vi} European Medicines Agency. Human medicines highlights 2019, https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2019_en.pdf

^{vii} World Intellectual Property Organisation. Patentscope database: <https://patentscope.wipo.int/search/fr/search.jsf>

^{viii} McClellan M. et al. Ibid

^{ix} Landray M. et al. Improving public health by improving clinical trial guidelines and their application, European Heart Journal, Volume 38, Issue 21, 2017

^x Fordyce, C. B. et al. Cardiovascular drug development: is it dead or just hibernating?, Journal of the American College of Cardiology, Vol. 65, 2015

^{xi} Landray M. et al. Ibid

^{xii} Cave A. et al. Real-world data for regulatory decision making: challenges and possible solutions for Europe, Clinical Pharmacology & Therapeutics, Volume 106, Issue 1, 2019

^{xiii} Postema P.G. et al. Continued misuse of orphan drug legislation: a life threatening risk for mexiletine, European Heart Journal, 2020

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