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Transferable data exclusivity vouchers are not the solution to the antimicrobial drug development crisis: a commentary on the proposed EU pharma regulation

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INTRODUCTION

Access to pharmaceutical products worsened during the COVID-19 pandemic when key developers of active pharmaceutical ingredients and medicinal products prioritised their national markets. These challenges led to a stronger commitment by the European Union (EU) to become more autonomous in developing and providing access to pharmaceutical products for its population.[1]

In April 2023, the European Commission (EC) proposed a reform of the EU pharma regulation to improve patient-centredness, strengthen the European pharmaceutical industry and incentivise pharmaceutical innovation.[1] This reform needs to be approved by the European Parliament. In its present form, it includes the introduction of Transferable Data Exclusivity Vouchers (TDEVs) to address the crisis in antimicrobial innovation. In this commentary, we assess the use of TDEVs as an important element of the EC's proposed pharma strategy on antimicrobial resistance (AMR).

SUMMARY BOX

- ⇒ Antimicrobial resistance (AMR) is a global and European challenge leading to avoidable deaths and high health system costs.
- ⇒ In order to spur antimicrobial innovations, the European Commission proposes the use of Transferable Data Exclusivity Vouchers (TDEVs) as an integral part of the 2023 EU pharma reform: incentivising antimicrobial development by granting data exclusivity on any drug of the manufacturer's choice.
- ⇒ TDEVs imply maintenance of high costs for other drugs without guaranteeing that needed novel antimicrobials against multidrug resistant microbes are developed and produced.
- ⇒ Delinking incentives from drug prices and offering a combination of push mechanisms and pull mechanisms should be considered by European policy-makers to increase the proposed EU pharma reform's impact and sustainability on overcoming AMR.

AMR: A SERIOUS CONCERN FOR THE EU AND GLOBALLY

Addressing AMR is one of the key objectives of the EU's pharma regulation reform. AMR constitutes one of the most important health threats in the EU, leading to 35 000 deaths annually and costing member states' healthcare systems €1.5 billion per annum.[2] The EU published its first action plan against the rising threat of AMR in 2011; the WHO its Global Action Plan in 2015,[3 4] with both bodies having discussed suitable interventions decades prior to these publications. AMR is clearly not only a major European threat but a severe global problem with 10 million people estimated to die from AMR by 2050.[5] A comprehensive analysis of the AMR burden in 204 countries estimated that worldwide 4.95 million deaths were associated with AMR in 2019,[6] with the highest burden of hospital-associated AMR in middle-income countries.[7] Sustainable solutions must, therefore, be on a global scale and transcend European boundaries.

In its 2023 reform, the EC proposes to reduce AMR through the following measures: (1) a One Health approach, highlighting (2) prudent use of antimicrobials (eg, rational prescriptions for humans, and reducing antibiotic sales for farm animals and aquaculture by 50%); (3) improved access and affordability of antimicrobials; (4) global cooperation and

support of WHO's new Pandemic Accord for prevention, preparedness and response, and keeping AMR a key issue for the implementation of the EU's Global Health Strategy and (5) research and technological innovation with TDEVs as an incentive for developing innovative antimicrobials.[1 2]

TDEVs FOR ANTIMICROBIALS

The EC proposes to offer TDEVs to manufacturers who develop novel antimicrobials. The vouchers grant manufacturers an extra year of data exclusivity on any one of their drugs and the possibility to sell the voucher to developers of other medicines.[1] The proposal foresees an evaluation after 15 years (ibid). Data exclusivity guarantees a market monopoly by barring competitors from registering a generic or biosimilar product. WHO's expert working group on research and development concluded already in 2012 that data exclusivity does not contribute to innovations in worldwide needed medications.[8]

While the EC specifies that the vouchers are restricted to 'game-changing antimicrobials that address AMR and the priority pathogens recognised by WHO',[1] WHO bemoans in its 2021 report that only 6 out of 27 antibiotics that are being developed for addressing priority pathogens, fulfil at least one innovation criteria and only two are active against multidrug resistant bacteria. Eighty per cent of 'novel' antibiotics belong to classes which easily lead to cross-resistance.[9] The EU should thus ensure that newly developed antimicrobials have a clear clinical benefit over existing ones before granting the manufacturer a TDEV.

In order to effectively combat AMR, the drugs need to be available and be used prudently not just in a few countries, but everywhere. Analyses for antibiotics have shown that most new drugs are registered initially in higher-income countries with low and delayed availability in low-income and lower-middle-income countries.[10] Even in high-income countries, we see a disparity in drug availability. Of 18 new antibiotics approved between 2010 and 2019, 17 were commercially launched in the USA; in Canada, by contrast, only two.[11] Of the 14 new antibiotics approved by the European Medicines Agency, 10 or more were launched in the UK and Sweden, whereas in other European countries, many remained unavailable (ibid). The absence or delay of commercial launches may be attributable to the underlying problem that has hampered the development of antimicrobials in general: low profitability because of generally low prices and short usage periods for antimicrobials.

The voucher system is a profitable reward system for manufacturers, who can stretch the reach of this system towards extending monopolies on their financially lucrative medicines. This, in turn, will lead to cost increases for health systems and will delay the availability of cheaper generic or biosimilar compounds of these drugs.[12–14] This was already foreseen in 2016 in an AMR review.[5] In short, vouchers would 'push the cost of antibiotic development onto an arbitrary set of payers and patients (those who use the medicines on which the voucher is applied)' (ibid). The actual societal costs of these vouchers are likely much higher than projections on which the EU seems to be basing their model.[12 13]

Notwithstanding the importance of other EU proposed measures, the voucher system will likely increase medicine prices and block generics from coming into the market. It may also not produce much benefit in terms of generating truly novel antimicrobials, the ultimate aim of the voucher incentive. This is also the stance of a non-paper (in-official document or discussion paper for negotiating positions within the EU) led by the Netherlands and supported by 13 European countries that critique the voucher system for 'stifl(ing) innovation from competitors and delay(ing) the introduction of generics' and likely bringing 'high costs to national systems'.[15] Beyond academics and politicians, further critique comes from non-governmental organisations and other civil society actors (https://medicineslawandpolicy.org/2023/03/how-not-to-solve-a-crisis-the-european-commissions-plan-for-transferable-data-exclusivity-vouchers/ (accessed: 17.10.2023); https://www.msfaccess.org/msf-responds-european-commissions-proposal-revise-eus-pharma-legislation (accessed: 09.08.2023); Buko Pharmabrief, May 2023).

OFFERING INCENTIVES DELINKED FROM SALES BUT CLOSELY LINKED TO THE CLINICAL VALUE OF THE DRUG

In view of the concerns highlighted above, the focus should switch towards alternative mechanisms. We suggest to include push incentives and pull incentives.[16] First, up-front funding should 'push' early and preclinical research and development as recommended in the Health Emergency Preparedness and Response (HERA) report[17], and provide adequate resources for basic and clinical research for AMR in general.[12 14] Second, 'pull' mechanisms, mentioned by the EC,[1] are set out in more detail in the HERA report[17]: They include the Annual Revenue Guarantee Scheme as a top-up to market sales. This can have different levels of guaranteed financial EU support based on the public health benefits of the drug innovation (ibid). Other pull incentives are market entry rewards, or a milestone-based reward for phases I and II of the drug development.[1 17]

Antimicrobial drug development lends itself to delinking incentives for innovation from the selling price of the drug. Delinkage could be implemented through direct financing and milestone prizes and possibly combined with purchase commitments to secure market prospects, thus combining push mechanisms and pull mechanisms to incentivise the development of innovative antimicrobials. Some critics also suggest to charge manufacturers an additional marketing authorisation fee for all non-antimicrobial medications which would then supplement market entry funding for antimicrobials.[14]

CONCLUSION

EU policy-makers need to carefully review the proposed EC pharma regulation reform with its important objective of effectively tackling AMR as a Global Health emergency. The pros and cons of possible solutions to incentivise antimicrobial innovation need ultimately to be scrutinised on the basis of their public health benefits. TDEVs seem the least likely to produce the desired results.

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