Transferable Exclusivity Vouchers and Incentives for Antimicrobial Development in the European Union

Health Policy Portal

Victor L. Van de Wiele,[1] *Adam Raymakers,*[1] *Aaron S. Kesselheim,*[1] *and Benjamin N. Rome*[1]

1. PORTAL, HARVARD MEDICAL SCHOOL, BOSTON, MA, USA.

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Abstract: The European Commission's proposal to address antimicrobial resistance using transferable exclusivity vouchers (TEVs) is fundamentally flawed. European policymakers and regulators should consider alternatives, such as better funding for basic and clinical research, use of advance market commitments funded by a pay-or-play tax, or enacting an EU Fund for Antibiotic Development.

In 2019, nearly 5 million deaths globally were associated with infections from bacteria with antimicrobial resistance (AMR).[1] Despite the growing need for effective drugs treating patients with infections from resistant bacteria, the development pipeline is limited, and few new antibiotics offer substantial benefits over existing options.[2]

Global concern over antibiotic innovation has led policymakers to consider a range of solutions. In June 2022, the European Commission (EC) released a report that suggested offering transferable exclusivity vouchers (TEVs) to encourage development of new antimicrobial drugs. TEVs have been proposed in other contexts, but given the EC's renewed interest, we review the parameters of a TEV and their strengths and limitations as a tool for the EC's to enhance antimicrobial innovation. We conclude that the EC conception of TEVs suffers from the same problems with cost and inefficiency that have undermined such proposals in the past.

The European Commission Proposal on TEVs

The version of TEVs proposed by the EC would grant manufacturers of new antimicrobial products—including antibiotics, antivirals, and antifungals—a voucher that would entitle the holder to an additional year of regulatory exclusivity for the drug of its choosing. To understand the premise of TEVs, it is important to recognize that brand-name drugs are sold by their manufacturers for high prices during market exclusivity periods protected by two different kinds of exclusivity. So-called regulatory exclusivity prevents drug regulatory authorities like the European Medicines Agency (EMA) from approving a generic or biosimilar version of the drug for a specified period of time, and typically serves as the floor for the length of market exclusivity. In addition, all new drugs are protected by patents that last 20 years from the date of filing and protect aspects of the drug like its active ingredient, formulation, and use. European Union Law also allows

Victor L. Van de Wiele, LL.B., LL.M., *is an affiliated researcher at PORTAL and a current PhD Candidate in Law at the University of Cambridge.* **Adam Raymakers, M.Sc., Ph.D.,** *is postdoctoral research fellow with PORTAL.* **Aaron S. Kesselheim, M.D., J.D., M.P.H.,** *is a Professor of Medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital. Within the Division, Aaron created and leads the Program On Regulation, Therapeutics, And Law (PORTAL).* **Benjamin N. Rome, M.D., M.P.H.,** *is an Instructor at Harvard Medical School, Division of Pharmacoepidemiology and Pharmacoeconomics and a faculty member in PORTAL.*

About This Column

Aaron Kesselheim serves as the editor for Health Policy Portal. Dr. Kesselheim is the *JLME* editor-in-chief and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women's Hospital/Harvard Medical School. This column features timely analyses and perspectives on issues at the intersection of medicine, law, and health policy that are directly relevant to patient care. If you would like to submit to this section of *JLME*, please contact Dr. Kesselheim at akesselheim@bwh.harvard.edu.

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manufacturers, European Union law allows manufacturers to extend one key patent associated with a drug up to five years via a supplementary protection certificate (SPC). A drug's key patents are usually obtained closer to when it was originally synthesized, but in nearly all cases, the actual scope of patent protection at the time of approval includes numerous overlapping patents. Studies have shown that a drug's patent protection usually last about 14-16 years after regulatory approval, or longer—for example, the macular degeneration drug aflibercept was approved in 2012 by the EMA but has patent protection until at least 2038.[3]

Extending market exclusivity and delaying generic or biosimilar competition by obtaining additional patents or regulatory exclusivities can be very lucrative for drug makers. A manufacturer awarded with a TEV could apply the voucher to one of its own drugs (likely the one with the highest revenue) or could sell the voucher to a different manufacturer. The idea is that the value to the company created by extending a drug's market exclusivity would provide monetary incentive to "pull" drug companies towards antimicrobial development. This contrasts with policies that "push" the development of new antimicrobials forward, such as dedicating more funding for basic or clinical research.[4]

To calculate the economic value associated with introducing vouchers,[5] the Commission conducted an impact assessment in which it estimated the costs and benefits of vouchers. For example, it calculated that if 3 vouchers were granted per year, the antimicrobial developers could sell them for a combined €500m. The extended market exclusivity for the drugs benefiting from the vouchers would lead to an additional €561m per year in health care spending.[6] If only one voucher was sold per year, antimicrobial developer revenues would amount to €413m. This would result in €294m of excessive healthcare spending per year. The report did not calculate the revenues for one voucher every two years because it did not envision this scenario's financial viability.[7] The study concluded the economic benefits of TEVs outweigh the costs.

The current EC proposal is similar to a previous legislative proposal submitted to the US Congress: the Re-Valuing Anti-Microbial Products (REVAMP) Act of 2018. This bill would have provided manufacturers of qualifying antimicrobials with a TEV that could be redeemed for 12 additional months of market exclusivity added onto the end of a drug's patent portfolio.[8] One analysis found that had such vouchers been granted to the 10 most recently-approved antimicrobial drugs, the additional exclusivity when applied to the top-selling drugs at the time would have resulted in $4.5 billion additional societal spending.[9] The bill was not considered by all members of the US Congress and has not been reintroduced in subsequent legislative sessions.

Problems with TEVs

Several well-known limitations with TEVs also apply to the EC's TEV proposal. First, the societal benefit of new antimicrobials may not justify the high societal costs of TEVs. The European Public Health Alliance recently argued, "There is a high risk that a TEV would overcompensate and give a disproportional reward to drug developers while not addressing the real obstacles to the development of a 'healthy pipeline.'"[10] While the goal is that developing new antimicrobials will have societal benefits including lives saved and reduced spending on complex infections, there is no guarantee that any one new antimicrobial will provide enough societal benefit to justify the high cost of the TEVs. Recently, fourteen EU Member States spoke out against TEVs because they are "an indirect non-transparent form of financing that stifle innovation and block generic competition."[11]

Second, TEVs lack ability to incentivize particularly important antibiotic development. In the past decade, most new antibiotics have been approved based on non-inferiority to existing products and hence do not show additional clinical benefits in patients with resistant infections.[12] If such new antibiotics received TEVs, it would fail to reward manufacturers for contributing to the public health goal of developing new therapies for the most severe resistant infections. Also, antimicrobials that receive a voucher are not guaranteed to incentivize important antibiotic development because they could be removed from the market for safety reasons or lack of profitability (as many have been over the last 3 decades), even after a TEV is granted.[13]

In addition to these well-known limitations, the European Commission's TEV proposal introduces several new concerns. First, the proposed vouchers would extend regulatory exclusivity, not patent protection. Patent protection is nearly always the determining factor in length of market exclusivity, particularly for blockbuster drugs. This limitation means that the TEVs proposed by the EC might not provide added revenue for most drugs. Concerningly, the impact assessment report of the proposed policy appears to assume that vouchers would only be sold to drugs that are not granted SPCs, but the Commission indicates that drugs with SPCs "tend to have high peak sales" and will be most attractive for TEV purchasers on which to apply the extra year of exclusivity.[14] For instance, an Irish Patent Office SPC database estimates that approximately 1000 drugs were covered by an SPC with an expiry date beyond January 2021, covering various drugs with blockbuster sales.[15] If only manufacturers of old drugs with expired patents and SPCs were interested in purchasing the TEVs, it would be difficult for awardees to sell these vouchers for the billion dollar price that was quoted by the EC to optimize antimicrobial drug development.[16] In this case, the voucher system fails to accomplish anything meaningful while adding more administrative and bureaucratic burden.

Better Incentives for Antimicrobial Development

Some commentators have offered certain guardrails that the EC can integrate into TEVs, but even these

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are insufficient solutions. For example, one suggested the Commission consider variable lengths of the voucher based on the level of clinical benefit of the antibiotic and sufficient advance notice to protect generic manufacturers. Limits on the length of the voucher as well as the financial reward accompanying it would then be proportionate to the clinical benefit associated with the drug.[17] Alternatively, Dubois et al. suggest that the regulator set the financial award level and that potential buyers bid the extension length for which they are ready to pay the reward, with the shortest extension length winning the auction.[18] But both proposals might result in TEVs that are so short that they offer no real financial incentives in the first place and continue to cause disruptions in the market to which they are applied.

While TEVs are not the solution to antimicrobial resistance, alternative mechanisms may offer better promise to help support innovation in this area. First, the Commission could offer financial support for antibiotics research and development. Funds could be generated by raising taxes or restructuring existing EU health care policy budgets to pay for antibiotic discovery efforts and clinical trial funding. For example, a "pay or play tax" would require that EU Member States pay the tax to receive access to antimicrobial products procured by the Commission. But such a proposal would also need to consider proportional measures that take into account the size, gross domestic product, and antibiotic needs of individual Member States.

Another option is a market entry reward, such as an advance market commitment in which EC Member States coordinate to buy a certain number of units of promising antimicrobials at a pre-negotiated price. This model takes into account existing market prices and supplements manufacturer revenues with additional revenues to make development profitable. This approach was used by the US to pay for the initial rounds of Covid-19 vaccines, achieving prices comparable to other vaccines.[19] Advance market commitments "de-risk" the drug development process and assure adequate access once a drug is approved at a fair price. Additionally, this approach delinks manufacturer revenue from the number of patients who use the drug, assuring adequate returns on investment while allowing antibiotics to be reserved for the relevant cases and removing manufacturer's incentive to market and encourage overuse.

While the above ideas focus on improving the development of new antimicrobials, it is equally important to focus on reducing unnecessary use of existing antibiotics to reduce the burden of AMR. For example, the EC could promote the creation of an EU Anti-Microbial Resistance Fund that provides research grants for academia and industry and secures a supply of antibiotics resistant to superbugs. It could resemble the UK's NHS Antimicrobial Stewardship Programme,[20] which offers hospitals financial incentives to reduce inappropriate prescribing through the involvement of pharmacists and clinicians reviewing prescription decisions. These pharmacists and clinicians also receive payments for gathering and sharing evidence of antibiotic consumption, and review within 72 hours of treatment initiation.[21]

The European Commission's proposal to address antimicrobial resistance using TEVs is fundamentally and irredeemably flawed. The vouchers would be inefficient, administratively burdensome, and would not provide an effective or relevant incentive. Instead, European policymakers and regulators should consider alternatives, such as better funding for basic and clinical research, use of advance market commitments funded by a pay or play tax, or enacting an EU Fund for Antibiotic Development.

Conclusion

The European Commission's proposal to address antimicrobial resistance using TEVs is fundamentally and irredeemably flawed. The vouchers would be inefficient, administratively burdensome, and would not provide an effective or relevant incentive. Instead, European policymakers and regulators should consider alternatives, such as better funding for basic and clinical research, use of advance market commitments funded by a pay or play tax, or enacting an EU Fund for Antibiotic Development.

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