

ANTIBIOTIC INCENTIVES IN THE REVISION OF THE EU PHARMACEUTICAL LEGISLATION

JOINT POSITION PAPER

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This paper was drafted by EPHA and ReAct Europe, and reviewed by the Steering committee of the A2M Task Force (Association of European Cancer Leagues). Endorsing organizations are listed at the end of the paper.

"It is critical that the implementation of any pull incentive is viewed in the overall context of the global strategy to combat antimicrobial resistance. The balance of promoting and rewarding innovation while ensuring patient access and aligning stewardship and public health objectives is necessary in the design of any successful pull incentive".¹

In its current revision of the EU pharmaceutical legislation, the European Commission (EC) plans to address the increasing burden of antimicrobial resistance (AMR) by setting up incentives for the development of new antibiotics. However, with only a few policy options considered during the consultations, there is a significant risk that a narrow and inefficient alternative such as a transferable exclusivity extension (TEE) is included in the EC proposal while an important opportunity to explore effective solutions is squandered. A thorough assessment of antibiotic incentives in the EU pharmaceutical legislation is therefore urgently needed.

In this short paper, we analyse the available research on the TEE and conclude that it will be a very inefficient and inequitable choice for the EU and the world, potentially exacerbating the AMR problem. Higher costs for medicines affected by a TEE would also be counterproductive in the current context of spiralling inflation and raising food and energy prices. The EC must ensure that the benefits of any new incentive surpass their potential costs, and that any EU incentive is compatible with other global, EU and national efforts. A starting point should be the wealth of evidence generated by experts, including several EU-funded projects addressing antibiotic incentives. Existing evidence overwhelmingly points against the TEE. Instead, the scarcity of new antibiotics calls for a holistic approach combining incentives to push and pull new antibiotics to the market, and the evidence points towards more efficient solutions such as the use of push funding and milestone prizes and the key role of the European Health Emergency Preparedness and Response Authority (HERA) as a pipeline coordinator.

¹ Årdal C, Røttingen J., Opalska A., Van Hengel A., Larsen J. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance, Clinical Infectious Diseases, Volume 65, Issue 8, 15 October 2017, Pages 1378–1382
<https://doi.org/10.1093/cid/cix526>

A TRANSFERABLE EXCLUSIVITY EXTENSION WILL CREATE HIGHER SOCIAL COSTS THAN BENEFITS

The transferrable exclusivity extension (TEE) has been presented primarily by pharmaceutical companies² as an efficient pull incentive. A TEE would provide a company that brings a new antimicrobial to the market with a transferable right, allowing it to extend the exclusivity period for another product. Such right could also be sold to another company to be used on a product in their portfolio. The TEE works under the assumption that such extension, by delaying the entry of generic competition, will bring a large monetary reward sufficient to provide incentives for companies to accelerate the development of new antibiotics. The option might appeal to EU policymakers as it does not require any budget commitment upfront and falls within EU competences. However, a wide majority of academics and expert studies have warned against the introduction of a TEE, finding significant drawbacks:

- 1. A TEE will create additional excessive social costs, which will directly affect European patients and national payers.**³ The TEE will delay the introduction of generic and biosimilar competition for the most profitable medicines ("blockbusters") as these are the most likely recipients of the exclusivity extensions, with considerable additional costs for national healthcare systems. According to Årdal et al, the cost of one new antibiotic to the European Union would be US\$ 3.2 billion.⁴
- 2. A TEE is ethically questionable as one therapeutic area will be subsidized at the expense of another.** A TEE could be extended to rare diseases or oncological therapeutics further worsening access to these medicines and adding additional barriers and increasing healthcare expenses.⁵
- 3. The TEE presents significant risks of overcompensation and disproportional reward for drug developers.** It has been estimated that 1 year of additional exclusivity for the Adalimumab and Trastuzumab blockbusters would respectively result in €1 billion and €600 million in additional costs for EU healthcare systems.⁶ A financial model developed jointly by the WHO and European Investment Bank to model the cost and risk, of antibiotic development estimated that the full end-to-end cost of developing one new antibiotic is 162.9 million USD, with an expenditure of 122.4 million USD for post launch commercialization and additional studies.⁷ The reward offered by the TEE is not proportional to the research and development costs.⁸
- 4. The TEE will cause additional problems of predictability of financing for EU healthcare systems.** The value of a TEE will be based on the drugs sold by the company that holds it. Hence, its value will not be known in advance, and this could result in a lack of predictability for European payers. While it has been suggested that the value of a TEE could be capped by insurers, the fragmented nature of EU healthcare systems further deters this option.⁹

2 <https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf>

3 Rome BN, Kesselheim AS. Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2020 Oct;71(7):1671-1675. DOI: 10.1093/cid/ciz1039.

4 Årdal C, Lacotte Y, Ploy M., (European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections, EU-JAMRAI), Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe, Clinical Infectious Diseases, Volume 71, Issue 8, 15 October 2020, Pages 1994-1999, <https://doi.org/10.1093/cid/ciaa153>

5 Årdal et al., 2017. op. cit.

6 Medicines for Europe. Note on Transferable Vouchers, April 2022 <https://www.medicinesforeurope.com/wp-content/uploads/2022/03/Med-for-Europe-Note-on-Transferable-Vouchers-April-2022.pdf>

7 A financial model for an impact investment fund for the development of anti-bacterial treatments and diagnostics. World Health Organization. June 1, 2020. See: <https://www.who.int/publications/m/item/a-financial-model-for-an-impact-investment-fund-for-the-development-of-antibacterial-treatments-and-diagnostics>

8 Outterson and McDonnell, 2016, op. cit.

9 Årdal et al., 2020, op. cit.

5. **The TEE would primarily favour large companies and only secondarily small and medium enterprises (SMEs).** This is despite the fact that SMEs and academia account for 92%¹⁰ of the actors involved in pre-clinical antibiotic research. Market-driven incentives that provide a reward only upon market entry, such as the TEE are less favourable to smaller entities that need direct payments to overcome initial research and development (R&D) barriers. What SMEs would need are adequate rewards earlier and throughout the whole R&D value chain, for example in the form of milestone payments, an alternative pull incentive that should be assessed.¹¹
6. **A TEE risks allowing a weak link between the value of innovation and its rewards.** A TEE could be granted to antibiotics with no significant therapeutic added value. Whereas high standards would be needed to ensure that only truly novel, innovative and efficient antibiotics benefit from a TEE, this would add another layer of complexity for regulators, potentially creating loopholes and inefficiencies in the EU pharmaceutical legislation.¹²
7. **A TEE does not ensure patients' access to the new antibiotic brought to market.** The TEE is designed as a one-off transaction at the marketing authorization point. Hence, companies will be free not to place products in some EU markets, to withdraw their products from the market due to commercial or manufacturing reasons, or products could need to be removed for safety reasons.¹³ Risks regarding limited access can also arise if the incentive does not entail other obligations such as requirements for registration, licensing, provision of use guidance as well as affordability.
8. **The TEE does not consider the availability of viable compounds in the pipeline in early discovery and development to actually "pull" from.** The 2021 clinical pipeline contained 27 antibiotics active against the WHO priority pathogens. Of these, only 6 fulfilled at least one innovative criterion, and only 2 addressed multidrug-resistant (MDR) Gram- bacteria.¹⁴ Unless the EU uses an end-to-end approach and collaborates globally, an EU TEE is unlikely to spur the development of critically needed novel antibiotics.
9. **The TEE does not inherently ensure obligations of stewardship and appropriate use and would require that conditions and compliance stipulations be attached to the voucher to ensure appropriate use.**
10. **A TEE will set a bad precedent and can lead to huge social costs outside of the EU.** If the delay of more affordable generics due to the introduction of a TEE affects also other countries through free trade agreements (as it has often happened with pharmaceutical exclusivities), the risks of delayed access to needed therapies will also multiply in lower-income populations around the globe.¹⁵

¹⁰ 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022. <https://www.who.int/publications/i/item/9789240047655>

¹¹ Aagaard H., Malpani R., Zorzet A., ReAct report: "Ensuring sustainable access to effective antibiotics for everyone, everywhere – How to address the global crisis in antibiotic Research and Development", <https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf>

¹² <https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance>

¹³ Årdal et al, 2017, op. cit.

¹⁴ 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022. <https://www.who.int/publications/i/item/9789240047655>

¹⁵ Outterson K., McDonnell A. Funding Antibiotic Innovation with Vouchers: Recommendations on how to strengthen a flawed incentive policy. *Health Aff (Millwood)*. 2016 May;135(5):784-90. doi: 10.1377/hlthaff.2015.1139.

CONCLUSIONS AND RECOMMENDATIONS

While a TEE might appeal to the EU as a legally feasible option within the revision of the EU pharmaceutical legislation as it does not require upfront investments from the public, most studies so far conclude that the potential costs of the vouchers will grossly exceed any potential benefits. Setting up a TEE without addressing why there is a scarcity of new candidate antibiotics in the pipeline will not facilitate the development of the antibiotics needed to address current and future health challenges. Considering that lack of access to antibiotics kills ten times more people worldwide than resistance to antibiotics,¹⁶ sustainable access to both existing and new effective antibiotics must be seen as a cornerstone of the EU and global health systems.

The complex failure in the market for new antibiotics calls for an EU coordinated approach addressing the problem from the beginning to the end of the R&D process. Rather than seeking to identify longer-term or permanent regulatory revisions for the introduction of a highly contested and untested incentive such as the TEE, the EU should pursue more comprehensive solutions (involving both push and pull incentives). Such incentives should facilitate the demand for public return on public investment and enable governments to exercise better control over research priorities and outcomes. Different studies have identified the use of milestone prizes¹⁷ and the role of the EU Health Emergency Preparedness and Response Authority (HERA) as a "*pipeline coordinator*" to shape and speed up the development of new antibiotics as more efficient alternatives.¹⁸ Likewise, the creation of a European medicines public infrastructure could provide a more stable solution for antibiotics and other areas of low commercial interest.¹⁹ While some of these solutions do not fit in the pharmaceutical legislation, we should keep in mind that the main goal of the revision should be to facilitate the development of new antibiotics in the most efficient way, synergistically and consistent with other EU policies.

¹⁶ DRIVE-AB Report. Revitalizing the antibiotic pipeline: Stimulating innovation while driving sustainable use and global access, 2018, <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>

¹⁷ Baraldi, E., Ciabuschi, F., Callegari, S., Lindahl, O. (2019). Economic incentives for the development of new antibiotics: Report commissioned by the Public Health Agency of Sweden. <http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-375258>

¹⁸ https://eu-jamrai.eu/wp-content/uploads/2021/07/1.3.1_Policy_brief_Improving_access_to_essential_antibiotic.pdf

¹⁹ [https://www.europarl.europa.eu/RegData/etudes/STUD/2021/697197/EPRS_STU\(2021\)697197_EN.pdf](https://www.europarl.europa.eu/RegData/etudes/STUD/2021/697197/EPRS_STU(2021)697197_EN.pdf)

ABOUT THIS PAPER

This paper was drafted by EPHA and ReAct Europe and reviewed by the Steering committee of the A2M Task Force (Association of European Cancer Leagues).

The following organizations have endorsed this paper:

1. European Public Health Alliance (EPHA)
2. ReAct Europe
3. Association of European Cancer Leagues
4. Consumer Association the Quality of Life-EKPIZO, Greece
5. Asociación por un Acceso Justo al Medicamento, Spain
6. Access to Medicines Ireland
7. Prescrire
8. Health Action International (HAI)
9. European Association of Hospital Pharmacists



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