

A new EU pull incentive to address Anti-microbial Resistance (AMR)

Recommendations from EFPIA

There is consensus globally on the scale of the challenge that anti-microbial resistance (AMR) represents for society and the need for novel anti-microbials to address the current patient unmet need.¹ The World Health Organisation (WHO) has declared that AMR is one of the top 10 global public health threats facing humanity.² There is broad agreement that the current model for incentivising new anti-microbials is not working and the pipeline is insufficient to tackle AMR. To fight AMR, urgent policy changes to promote the development of novel anti-microbials are needed.³ Concrete actions must be taken at the global, regional and country levels. Although AMR is a global challenge, the world's leading economies, including the European Union (EU) need to provide leadership on the implementation of policy solutions. This includes a package of push and pull incentives to deliver a sustainable, robust pipeline of new anti-microbials.⁴

This call to action is reflected in several recent EU initiatives. AMR is a key priority in the Pharmaceutical Strategy for Europe⁵ and the Horizon Europe research calls for 2021-2022 include a request to develop work that prepares for a European pull incentive for new anti-microbials.⁶ The newly-established Health Emergency Preparedness and Response Authority (HERA) was also designed to complement current EU efforts in addressing AMR.⁷ Although these initiatives represent important steps, further action is needed to address the market failure for anti-microbials so as to drive sustained private research and development (R&D) investments in this critical field. To achieve this objective, **we call for the development of a new incentive at the EU level in the form of a transferable exclusivity extension (TEE).**

A new incentive proportional to the scale of the AMR threat

To revitalize anti-microbial R&D, it is essential to reward successful innovation at a level that is sufficient to attract the investment required and incentivise companies to take on the substantial risks of anti-microbial R&D. The concept of TEE has been discussed in the expert literature for several years and proposed as a potential solution to address the current economic challenges constraining R&D in this field.⁸ A research-based company successful in bringing an eligible priority anti-microbial to the market, would be entitled to receive a transferable right to extend the exclusivity period of another product. This TEE could be applied either by the same company that developed the new anti-microbial within its own

¹ World Health Organisation (2020) "Lack of new antibiotics threatens global efforts to contain drug-resistant infections", Available at: <https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections>

² World Health Organisation (2020) "Antimicrobial Resistance", Available at: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>

³ Key stakeholders and studies have recognized the need for policy changes to develop new antimicrobials such as the following EU-JAMRAI Layman Report [here](#), DRIVE-AB "Revitalizing the antibiotic pipeline" [here](#), G7 Health Ministers' Declaration [here](#)

⁴ There is general consensus on the need for both push and pull incentives to stimulate antibacterial drug development. A mixture of incentives is needed to promote innovation in small, medium, and large enterprises developing multiple types of products capable of treating drug-resistant infections. "Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Anti-microbial Resistance", Årdal et al, Clinical Infectious Diseases, Volume 65, Issue 8, 15 October 2017, Pages 1378–1382, <https://doi.org/10.1093/cid/cix526>

⁵ EU Pharmaceutical Strategy for Europe (2020), Available here: https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf

⁶ "Development, procurement and responsible management of new antimicrobials" in Horizon Europe: Work Programme 2021-2022, https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2021-2022/wp-4-health_horizon-2021-2022_en.pdf

⁷ European Commission (2021) Available at: https://ec.europa.eu/health/sites/default/files/preparedness_response/docs/hera_2021_comm_en.pdf

⁸ Rome and Kesselheim (2020) "Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis", Available at: <https://pubmed.ncbi.nlm.nih.gov/31630159/>

portfolio or sold to another company. There are estimates of the expected scale of the incentive required and the implications for applying a TEE in the European context (please see Box 1 for a brief summary).

Box 1: Scale of the incentive required and impact of a TEE on the healthcare system

There is increasing expert literature estimating the size of the incentive required to boost the development of new anti-microbials. Outterson (2021) suggested that a global reward of \$2.2 – \$4.8 billion⁹ would be needed to incentivise a developer to take on the substantial risks and costs needed in anti-microbial R&D given the very limited commercial returns for any potential new anti-microbial.¹⁰

The Office for Health Economics (OHE) estimated that a European incentive needs to provide developers at least €280 million for a new product in an existing class of antibiotic product and €440 million for a new class of antibiotic product. This work is based on a series of assumptions around a ‘fair European share’ of the global pull incentive, in the context of other regions’ efforts and compared to what is required to incentivise R&D investment in new anti-microbials.¹¹

The same study suggests that if a TEE were to be implemented in the EU, based on the current pipeline and the pathogens targeted, around 1-3 TEEs could be expected per year over the next 15 years.¹² Depending on the number of TEEs issued per year, each voucher would generate net revenues between €350 million to €500 million to sellers, although some may sell for up to €800 million. If three TEEs were traded, this would suggest an estimated net cost of €460 million to €990 million.

As a new incentive, a TEE in the EU would have several significant advantages:

1. It can be implemented via EU-level legislation;
2. It does not require upfront government funding and is not dependent on a Member State’s economic situation or changes in the political situation;
3. It would address the failure of the current incentive framework by offering a potential incentive at the scale required to drive greater R&D in new anti-microbials and that recognizes their broader societal value;
4. It would support all pharmaceutical companies of all sizes, including small and medium sized companies (SMEs) as they would be rewarded as early as regulatory approval for a new anti-microbial. It would also increase the attractiveness of the anti-microbial field for private financing mechanisms, such as venture capital;
5. It is pro-stewardship and respects prudent use, leading to improved medical outcomes for patients by delinking financial reward from the volume of prescriptions, which underpins the standard R&D model;

⁹ Outterson, K. (2021) “Antibacterial R&D: Past, Present, & Future”, Available at: <https://www.hhs.gov/sites/default/files/day1-03-outterson.pdf>. This range will be updated in further work completed by Outterson, which will be published in November 2021

¹⁰ Based on Towse A, Hoyle CK, et al. Time for a Change in How New Antibiotics are Reimbursed: Development of an Insurance Framework for Funding New Antibiotics based on a Policy of Risk Mitigation. Health Policy, 121:1025-30, 2017 & Ardal C et al. DRIVE-AB Report: Revitalizing the antibiotic pipeline: stimulating innovation while driving sustainable use and global access. 2018. <https://amr.solutions/2020/04/14/pull-incentives-for-antibiotics-how-much-and-why/>

¹¹ “Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D”, A report by the OHE, December 2019

¹² Other studies have been conducted on the global pipeline of antibiotics that would lead to similar conclusions. An analysis by Pew Trusts (2021), suggests that around 43 antibiotics are in development and applying probability of success by each phase of development this would lead to approximately 15 new antibiotics. Additionally, a limited number of these represent novel classes and are active against key WHO critical threat pathogens. Pew study: <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development>; Probability of clinical success study: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226120/#:~:text=The%20success%20rate%20of%20each%20drug%20discovery%20stage%20in%20academia,%25%20\(Figure%20%E2%80%8B1\)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226120/#:~:text=The%20success%20rate%20of%20each%20drug%20discovery%20stage%20in%20academia,%25%20(Figure%20%E2%80%8B1))

6. It would be complementary with other EU and national initiatives, such as HERA and country-level health technology assessment (HTA) and reimbursement reforms; and
7. It provides an opportunity for the EU to lead in the development of a new form of incentive that could be replicated in other regions.

TEE would represent a unique solution addressing the challenge of AMR within a broader package of measures

There is currently broad consensus on the need for a package of both push and pull incentives to address the lack of new anti-microbials.¹³ Push incentives de-risk early research, while pull incentives support ‘end-to-end’ development including late-stage R&D and reward success for developing a new anti-microbial. These are complementary as they seek to address different barriers to the development of new anti-microbials, but ultimately need to work together. Significant progress has been made in the implementation of push incentives.¹⁴ However, a lack of pull incentives remains. The \$1 billion Global AMR Action Fund, launched by the biopharmaceutical industry and other partners in July 2020, shows industry’s commitment to advance stakeholder collaboration in the fight against AMR. The Action Fund aims to deliver up to four novel antibiotics by the end of the decade.¹⁵ This provides much needed short-term support, however it is only a bridging mechanism, recognising in its mission that further policy reforms are required to ensure a sustainable anti-microbial ecosystem.¹⁶ This can be achieved via a package of incentives, including pull incentives and HTA and reimbursement reforms of anti-microbials, to ensure market sustainability for these products.

Striking the right balance

TEE should be designed so that it provides an appropriate reward to incentivise R&D whilst aligning the value of the TEE with the broader societal value of the anti-microbial. This means that the value of the TEE would be based on the anti-microbial developed with the exclusivity extension duration being modulated for different classes and depending on the pathogen the medicine targets and its priority level.¹⁷ Additional requirements could be included in the TEE structure, such as the commitment to support appropriate anti-microbial stewardship, for example through an Antibiotic Management Plan agreed with the European Medicines Agency (EMA). This would mean that TEE incentivises new anti-microbials, encourages reliable supply and supports stewardship.

The TEE should also be designed in such way that it supports innovation, whilst ensuring that the end of the exclusivity period for the recipient product is predictable, so that TEE does not disrupt the business model of the generic market. It is reasonable that products “receiving” a TEE must have a reasonable remaining exclusivity period to provide appropriate predictability to the generic industry. However, if such period extends beyond two years, few other conditions should be imposed on the recipient product in order to increase competition, efficiency of TEE as a payment mechanism and predictability of the incentive. This would also help to ensure the size of incentive delivered through TEE reflects the value of the anti-microbials.

In addition, it is important to set out how TEE would work with other EU policy initiatives, such as joint procurement and stockpiling via the newly-created HERA and other EU pandemic preparedness initiatives. As announced in September 2021, HERA will have widespread responsibilities (monitoring, R&D, manufacturing, stockpiling, joint procurement) but given the

¹³ Ardal et al (2017) Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance, Available here: <https://academic.oup.com/cid/article/65/8/1378/3862465>

¹⁴ World Economic Forum (2018), “Antimicrobial Resistance: Tackling the Gap in R&D with Pull Incentives”, Available at: https://www3.weforum.org/docs/Antimicrobial_Resistance_pagers_2018.pdf

¹⁵ IFPMA’s “Global Principles on Incentivizing Antibiotic R&D” <https://www.ifpma.org/wp-content/uploads/2021/02/IFPMA-Global-Principles-on-Incentivizing-Antibiotic-RD.pdf>

¹⁶ AMR Action Fund, Available here: <https://www.amractionfund.com/about-us>

¹⁷ One way to do this would be to specify a range (minimum and maximum) - similar to the way it was constructed for the PASTEUR ACT in the U.S. Where the product will fall within the range will depend on value - which can be either assessed systematically or via a simplified checkbox process to achieve a point-based system.

budget allocated (directly €6 billion for all HERA activities during 2022-2027) and the range of responsibilities, it is unlikely that it will be able to incentivize anti-microbial R&D at the scale required. Hence, HERA-related initiatives do not replace the need for a new pull incentive such as a TEE but could complement it, depending on its structure. Indeed, EU joint procurement could be used as a mechanism to contract with anti-microbial providers and thereby increase the sustainability of the provision of anti-microbials.

Finally, while the TEE would incentivise and reward a successful R&D process for novel anti-microbials, in order to ensure sustainable access after regulatory approval, additional mechanisms are needed. This would require an appropriate approach to HTA and reimbursement reforms to ensure sustainable anti-microbial provision.

In conclusion, a package of policies is needed to address AMR at a global level and bring novel anti-microbials that will address high patient unmet needs. Different regions will develop incentives aligned to their healthcare systems and forms of governance. A TEE would offer significant advantages in the EU, would demonstrate EU leadership in the fight against AMR and would pioneer a mechanism that could be replicated in other regions. An EU TEE can serve as a complementary pull incentive mechanism to other incentives in the package such as the AMR Action Fund and the value assessment and reimbursement reforms at national level, supporting a sustainable access after launch. A TEE would also support broader initiatives that aim to improve surveillance, stewardship and EU-wide access and distribution of anti-microbials, which are key pillars in the fight against AMR.
