Response to call for public consultation

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Thank you for the opportunity to comment on the "European medicines agencies network strategy to 2025."

As experts and stakeholders in AMR, we limit our comments to section 3.4 Antimicrobial resistance and other emerging health threats. Six goals were outlined. We will focus on goals 4 and 5.

As context for our comments, we believe that Europe faces a pair of interlinked crises in antibiotic R&D.

First, ***the global economic model is fundamentally broken***. New antibiotics don't sell because stewardship puts them on the shelf. A good new antibiotic sells poorly; a great new antibiotic will sell even less. And yet we need them as fire extinguishers, providing preparedness and protection against bacterial threats.

The second crisis is more surprising: ***new antibiotics are not being registered or sold in Europe***. Given the poor economics, the small companies bringing many new antibiotics to market are focusing only on the US market and many of those are going bankrupt. Five of the last fifteen new antibiotics approved by the FDA in the past decade have gone through bankruptcy or near-zero valuations in the past two years. New drugs like omadacycline[3] and plazomicin[4] are not being registered in Europe, and lefamulin still awaits a commercial partner to launch in Europe[5]. Eravacycline, approved by EMA in October 2018, still has not been commercially launched in Europe. We can offer our speculation on drivers, but a full root cause analysis is needed. For lefamulin and plazomicin, a key driver appears to be the that the cost of EU-required pediatric trials exceeded any plausible estimate of sales in Europe, leading to the companies to withdraw from the process. These events suggest that it is likely that new antibiotics from small companies will not be available in Europe, much less the rest of the world.

Encouragingly, some of the elements of the "European medicines agencies network strategy to 2025" appear well positioned to address these two concerns.

Goal 4: Define pull incentives for new and old antibacterial agents, including investigating support for new business models and non-for-profit development.

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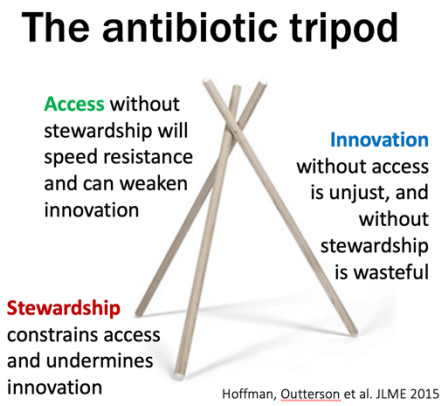
[3] https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/nuzyra.

[4] https://amr.solutions/2020/07/11/plazomicin-eu-marketing-application-is-withdrawn-near-zero-market-value-of-newly-approved-antibacterials/ and https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/zemdri.

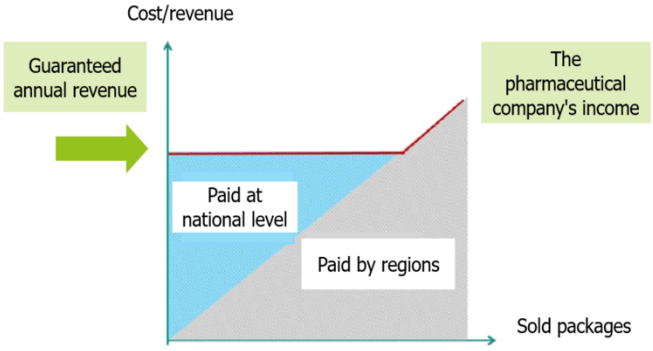
[5] Nabriva Therapeutics plc 10Q (June 30, 2020) https://www.sec.gov/ix?doc=/Archives/edgar/data/1641640/000155837020009653/nbrv-20200630x10q.htm.

After years of work supported by the European Commission through IMI (see the 2017 DRIVE-AB Final Report[6]), we should be well past the "investigating" phase and moving towards national or EU implementation. Pull incentives must be of sufficient magnitude to both (i) provide an innovation incentive for work in this area and (ii) cover the cost of product maintenance in this area. They should complement the work of key push incentives, and simultaneously support stewardship, access, and innovation.[7] One key finding from DRIVE-AB is that antibiotic pull incentives should be measured by value to society, not the volume of antibiotics sold in any given year, a concept called "delinkage" because rewards to the innovator are delinked from the volume of sales.



As an example of how this might be done, the pilot program at NHS England is very promising if made permanent, by offering an incentive payment of up to GBP 10m x 10 years for antibiotics meeting public health criteria. GBP 100 million (approximately US$130 million) over ten years is within the range of the UK's "fair share" (based on the UK's portion of the G20 economies) of a collective global pull incentive of $3-4 billion.[8]

The Swedish antibiotic access pilot[9] is an elegant model that could also work in many European national systems. Although, the SEK values in the Swedish pilot were selected with only access in Sweden in mind and are too low to provide a meaningful innovation incentive[10], the model is conceptually solid and these financial values could readily be adjusted upward to also function as an R&D pull incentive. By leveraging the insights from these pilot programs, the EU can contribute its fair share towards global antibacterial R&D through coordinated national pull incentives.



Despite the promise of these national projects, the small companies with antibiotics approaching approval would greatly benefit from a single "one and done" reimbursement access to EU markets. These companies lack the teams of people to navigate myriad national reimbursement schemes, leading some to abandon European markets altogether or significantly delay commercial launch.

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[6] http://drive-ab.eu/drive-ab-outputs/drive-ab-reports/.

[7] Hoffman SJ, Outterson K. What will it take to address the global threat of antibiotic resistance? Journal of Law, Medicine & Ethics. 2015;43(2):363-8.

[8] https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/.

[9] https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/.

[10] SEK 4 million, approximately US$460,000 per year. The Swedish pilot was explicitly designed to facilitate access in Sweden, not support global R&D as a pull incentive.

Beyond the larger issues of R&D, Europe must also find a way to cover the cost for important antibiotics for the required pediatric trials and other trials required as post-approval conditions of marketing approval. In the US, BARDA is available to pay for some of these costs, as evidenced by the recent $285 million contract to Paratek to support omadacycline,[11] but money to support European requirements should come from Europe. It has long been discussed among stakeholders that Europe lacks a mechanism like BARDA to support antimicrobial innovation.

Goal 5: Foster dialogue with developers of new antibacterial agents and alternatives to traditional antimicrobials, to streamline their development and provide adequate guidance in both human and veterinary medicine.

EMA has worked steadily to update its guidance documents for evaluation of medicinal products indicated for treatment of bacterial infections, and it is encouraging to see that a 3rd revision of this document is now underway.[12] The ongoing efforts of EMA to align with requirements from FDA (USA) and PMDA (Japan) are also noted with appreciation[13] as such efforts are fundamental to the design of the trials that can support approval in jurisdictions around the world.

These substantial efforts noted and acknowledged, works remains to be done on strategies to support the varied needs of developers in this area. A conference focused on enhancing the antibacterial trial process in the US was hosted 18-19 Nov 2019 by FDA, IDSA, NIH, and the Pew Charitable Trusts.[14] This conference highlighted potential actions for all stakeholders and a similar discussion in Europe involving such global and European stakeholders as the BEAM Alliance, CARB-X, the Novo REPAIR fund, GARDP, the Global AMR R&D Hub, and ESCMID would be informative and timely.[15] In addition to the topics already raised as part of the text of Goal 5, other topics to be covered should include strategies for products focused on rare pathogens, strategies for products focused on prevention, as well as other areas of concern raised in conversation with these stakeholders.

[11] https://investor.paratekpharma.com/news-releases/news-release-details/paratek-awarded-barda-project-bioshield-contract-nuzyrar.
[12] https://www.ema.europa.eu/en/evaluation-medicinal-products-indicated-treatment-bacterial-infections.
[13] https://www.ema.europa.eu/en/documents/minutes/meeting-summary-tripartite-meeting-held-between-pmda-ema-fda-kyoto-japan-discuss-convergence_en.pdf.
[14] https://amr.solutions/2019/11/27/18-19-nov-2019-fda-idsa-nih-pew-workshop-enhancing-antibacterial-trials-in-the-us/.
[15] https://beam-alliance.eu/, https://carb-x.org/, https://www.repair-impact-fund.com/, https://globalamrhub.org/, and https://www.escmid.org/.