Policy Position

Sustainable models to overcome the challenging economics of antimicrobial R&D

Background

A global consensus has emerged that antimicrobial resistance (AMR) is reaching a major crisis that will require concerted collaboration to effectively incentivize innovation, improve stewardship and strengthen access. Through the 2016 AMR Industry Declaration[1] and 2016 AMR Industry Roadmap[2] the pharmaceutical industry has recognized its responsibility to help address the various challenges related to AMR. This position paper focuses more specifically on the challenging economics of antimicrobial research and development (R&D).

New antibiotics, vaccines, diagnostics and adjunctive therapies are urgently needed to treat and prevent infections. The traditional economic market logic is ill-equipped to incentivize antibacterial innovation sustainably; although investments continue, they remain too few to address the current and future medical needs that result from AMR. In recent years, leaders in both the public and private sectors have called for market interventions to encourage sustainable investment in antimicrobial R&D. In this position paper, the IFPMA highlights a series of incentives and criteria for the development of a new economic model that would help foster a fertile environment for R&D and ensure that the growth of resistance is sustainably managed and controlled.

Key Issues

1. Push & Pull Incentives

Multiple incentives are needed across the development lifecycle of novel antibiotics and vaccines to stimulate R&D investment and address the lack of financial return for these products. While push mechanisms move research forward – they help "de-risk" companies' initial investments by pooling funds and expertise – pull mechanisms reward successful delivery of innovation with funding that increases the return on investment (ROI) and improves the predictability of the demand.

To date, a relatively significant amount of attention has been placed on the development of "push" mechanisms through research grants, such as through IMI, BARDA, NIH/NIAID and the CARB-X initiative.We also acknowledge and support the past and ongoing efforts made to improve and harmonize regulatory and approval pathways. These initiatives are valuable and should be continued. Complementary to these "push" mechanisms, and also of critical importance, are "pull" mechanisms, which reward the successful development of an approved medicine. These mechanisms would help provide sufficient return on investments to incentivize pharmaceutical companies to take on the necessary risk and uncertainty that comes with the development of new medicines (antibiotics and vaccines). Without significant pull mechanisms, there is a risk that the full impact of push funding would not be realized.

Given the long time horizon associated with developing medicines (antibiotics, antifungals, and vaccines) to address antimicrobial resistance, decisions taken today will influence the development and availability of treatment options 10 or 15 years from now. If recently-launched products (or those that will be launched in the next few years) are seen as commercial failures, it will continue to lead to further decrease in investments, and/or to the suspension of antimicrobial research and development by companies.

[1] AMR Industry Declaration, 2016, available at: http://www.ifpma.org/resource-centre/declaration-by-the-pharmaceutical-biotechnology-and-diagnostics-industries-on-combating-antimicrobial-resistance/
[2] AMR Roadmap, 2016, available at: http://www.ifpma.org/resource-centre/industry-roadmap-for-progress-on-combating-antimicrobial-resistance/

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2. Key principles to incentivize antimicrobial discovery and development

The following are key principles policymakers should consider when developing policies to incentivize antimicrobial discovery and development.

- **There is no "one size fits all" solution:** Although AMR is a global challenge, solutions should be tailored to different health systems and priorities. Global and regional coordination could help to identify priorities and facilitate regulatory processes.
- **Clear definitions for products that would earn a pull reward are needed**: To further incentivize R&D, the characteristics of new agents that would earn a "pull" reward should be developed.
- **Market-based models should be retained to allocate limited resources and reward successful innovation:** Competition and market forces remain an effective tool to incentivize the development of products that are best suited to meeting patients' needs (safety, efficacy, access). For antimicrobials, existing market-based systems can be refined to both incentivize antimicrobial innovation and reinforce antimicrobial stewardship and take into account public health goals.
- **Predictable and sustainable funding**:Given the time needed to develop new antibiotics and vaccines, the mechanisms put in place to support R&D should be predictable, reliable and sustainable to effectively incentivize investments.
- **The societal value of antimicrobial medicines (antibiotics and vaccines) should be reflected in the incentive model**: Antimicrobial medicines are undervalued by payers relative to the value they bring to society. Health Technology Assessments (HTA) frameworks need to account for this societal value and to address the challenges of demonstrating value of innovative antibiotics approved based on data from non-inferiority trials[3].
- **A return sufficient to justify ongoing investment of R&D resources:** Attractive and predictable prospects of ROI are needed to encourage further investments in R&D. The impact of these incentives will be determined by the specific type of R&D investment being considered, the value of other push-pull incentives that are available, as well as company-specific considerations.
- **Alignment with stewardship principles that support global access:** Efforts to incentivize sustainable investment in novel antibiotics should be aligned with initiatives by public and private stakeholders to ensure antibiotics are only used in patients who need them. The incentives should support mechanisms to facilitate affordable access to high-quality new and existing antibiotics, diagnostics and vaccines to the patients who need them.

3. Incentives building on existing systems

Opportunities for incentivizing antibiotic innovation may be present in existing systems. For example, **reimbursement reform** for hospital-administered antibiotics would remove barriers to access posed by bundled-payment mechanisms that discourage the appropriate use of novel antibiotics. This market-based mechanism can complement and reinforce key antimicrobial stewardship components, including the use of diagnostics, de-escalation, regimen monitoring, and surveillance. Payer reform is needed to better capture the societal value of antibiotics in HTA assessments.

Other opportunities may be found by building on existing legislation models. Several countries have successfully used push and pull incentives such as extended exclusivity, tax credits and others. This has helped support investment in R&D for diseases where market inefficiencies exist. Similar mechanisms could be used to stimulate development of novel antibiotics, especially those targeting currently rare but prioritized resistant pathogens.

While leveraging tools in existing systems can provide solutions in the short term, it will not be sufficient to sustainably address antibacterial innovation challenges.

[3] Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Outterson K. 2014 Analytical framework for examining the value of antibacterial products. Washington, DC: US Department of Health and Human Services/ASPE. https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products

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4. Novel incentive models

It should be acknowledged that there is a unique market dynamic for antibiotics, where new treatments should be used at a minimum level to avoid the build-up of resistance. The economic challenges related to AMR are different from the challenges encountered by other disease areas where market inefficiencies also exist. There is no "one size fits all" solution.

The pharmaceutical industry is engaging with stakeholders around the world to explore viable novel incentive mechanisms that both:

1) Reward innovation earlier in the product life cycle with the objective to help ensure that several treatment options are available to society to combat resistant infections.
2) Reduce the proportion of manufacturer revenue derived from antibiotic sales volume (often called "de-linked" or "partially de-linked" models referring to different options for the interaction between revenue and volume) while adequately incentivizing development, which is especially important for antibiotics that are likely to be used rarely or to be reserved for late-line use.

In the following section, we describe three novel incentive mechanisms. The IFPMA does not favor one model over the other rather the following options represent a menu of potential solutions which governments can use to overcome the various economic challenges related to AMR.

- **Market Entry Rewards** where the drug developer is rewarded for success in developing a drug targeting a prioritized pathogen by a payment or series of payments upon approval or other potential milestones. To be viable, such market entry rewards will need to be transparent, predictable and sustainable. We believe that to meet these criteria, these rewards must be awarded through processes in the key markets, such as the US, EU, and Japan, and possibly others, with coordination on priority targets and criteria. The developer would retain rights to the drug which would maintain market-based aspects to incentivize further development (some revenue from sales). The developer could also agree to conditions on stewardship, promotion, and global access in return for the market entry reward.

- Similarly, in an **Insurance License Model** a flat annual fee is negotiated directly with manufacturers and paid by relevant payers. Drug and biologics are either purchased in addition to the annual fee or a certain number of courses of therapy are included within the fee. In either case, the effective price perceived (or paid) by healthcare providers is set to be meaningfully higher than the cost of more general-purpose antibiotics. The price differential should be set in a way that reinforces stewardship without hampering access and appropriate use. To appropriately reward continued investment in innovation, a "graded array of benchmarked rewards designed to encourage the development of antibiotics and vaccines with the greatest societal value"[4] can be used to determine the annual de-linked payments to manufacturers.[5]Additional provisions could include reduced promotional activities by the manufacturer and a limit (cap) on the profit that can be earned in the event of demand requirements due to a catastrophic resistant infection outbreak that exceed a certain threshold.

- **Intellectual Property Mechanisms**, including transferable marketing exclusivity extensions, would improve the return on investment to justify investment of limited R&D funding for a drug or biologic targeting a prioritized Multi Drug Resistant pathogen. Any antimicrobial developer that meets market reward criteria would receive an exclusivity extension that could be used for another marketed product or wou be able to sell it to another company. Through this model, a substantial amount of the manufacturer revenue would be generated from the transferable marketing exclusivity, not the volume of antibiotic sold. Potential public health conditions or "guardrails" would be included to maximize public health benefit while minimizing downside risks.

The three above incentive model options will require additional consultation with industry and will need to be developed in more detail on a country-by-country basis to ensure their clarity and effectiveness going forward.

[4] For example, novel products would qualify for higher payments if they targeted priority pathogens, had a better safety profile, or were approved for special populations or in oral dosage forms.
[5] Rex JH, Outterson K. Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. Lancet Infect Dis. 2016 April;16(4):500–505.

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Recommendations

The challenge of AMR is enormous and urgent. The Davos Declaration from January 2016, signed by over 100 companies and trade associations, called for collective action to create a sustainable and predictable market for antibiotics, vaccines and diagnostics that enhances conservation for new and existing treatments. Coordinated action is needed to improve hygiene, prevention of infections, stewardship and conservation measures. Collectively, we need to seize the momentum provided by the UN, G-7, G-20 and the 32 national AMR action plans sponsored by governments around the world to move forward concrete actions on AMR.

1) We call on the G7 and G-20 governments to urgently address the economic barriers to antimicrobial R&D and ensure sustainable investment in a robust pipeline of innovative products (not just antibiotics, but also vaccines, diagnostics, and alternative therapies) targeting resistant pathogens through the implementation of a robust "pull" mechanism consistent with the principles described in this paper.

2) We call on the UN and Member States to continue and expand the formal collaboration between government, industry and other stakeholders to combat AMR by including the pharmaceutical industry in the mechanism to follow up on the commitments made in the Political Declaration of the High-Level Meeting on AMR. The pharmaceutical industry has an important role to play not just in R&D, but also in promoting stewardship and enhancing access. Work on AMR action plans at the global, regional, and national levels should formally include the pharmaceutical industry.

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