The role of the pharmaceutical industry in meeting the public health threat of antibacterial resistance

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**A B S T R A C T**

The established market model for pharmaceutical products, as for most other products, is heavily dependent on sales volumes. Thus, it is a primary interest of the producer to sell large quantities. This may be questionable for medicinal products and probably most questionable for antibacterial remedies. For these products, treatment indications are very complex and encompass both potential patient benefits, possible adverse effects in the actual patient and, which is unique for this therapeutic class, consideration about what effects the drug use will have on the future therapeutic value of the drug. This is because bacteria are sure to develop resistance. The European Federation of Pharmaceutical Industries and Associations (EFPIA) agrees with the general description of the antibacterial resistance problem and wants to participate in measures to counteract antibacterial resistance. Stakeholders should forge an alliance that will address the need for and prudent use of new antibiotics. A variety of incentives probably have to be applied, but having all in common that the financial return has to be separated from the use of the product.

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1. Basic conditions

Industry funds its investments in R&D by selling products at a relatively high price during a limited patent life. Patents are nominally 20 years, but once all the studies and paperwork are done, usually 10–12 years remain. Investment decisions are based on the cash-flow that can be generated once the product is on the market. The price is set to reflect the value of the product to society, including affordability and willingness to pay. This we call value-based pricing. However, these things do not work for new antibiotics. First, it is widely held in public policy circles that new antibiotics will be reserved and only gradually released to the market. The desire to focus the usage is understandable, but will reduce sales and hence reduce the ability of the innovator company to recover the costs required to bring that drug to the market. It can also be expected that public support for antibiotic research will be conditional on ensuring equal access to all citizens of the world and hence reduced value from sales in many emerging markets. For this reason, if we want to find a consensus, any public policy solution to the problem must:

- anticipate the impact of restricted, or at least agreed, use of new agents; and
- provide for global access to new medicines at a fair price.

Financial incentives for the private sector must be designed to address these challenges and meet these needs.

2. Changing from the past to the future

There is strong support among industry, physicians, pharmacists and others to combat antimicrobial resistance. However, for a number of reasons, it is difficult to expect changes in behavior here and now:

- Local subsidiaries of pharma companies, as well as local companies and generic players, generate cash-flow by selling today's antibiotics.
- Physicians and pharmacists worldwide are reluctant to reduce the use of antibiotics (patient pressure, revenue, risk of litigation, etc.).

Building on the need for change, new solutions should look to the future and aim for a global compact among all stakeholders to ensure that new medicines will not be introduced and used the way they were in the past. Fighting resistance through training of physicians, pharmacists and the general public will be an important priority for individual countries.
Forcing an alliance between all stakeholders will only work if it is realistic and addresses the need for, and prudent use of, new antibiotics. Therefore, I pledge to this conference that we need to separate the past from the future. Anything else will not be satisfactory.

A global compact (mirrored on the UN program for good governance and sustainable development) could focus on the agreed and gradual introduction and responsible marketing and use of new agents. This includes the need for differential pricing to ensure equitable access for all patients in need. The experiences from the HIV/AIDS must be harnessed. It is not reasonable that the least developed countries in the world pay as much as those with the highest income. A global compact would require that not only industry but also governments, physicians and pharmacists join forces to preserve the new medicines that our children and grandchildren need.

3. Incentives needed, but there is no general solution

Turning from principles to practicalities: what would work? How do we kick-start antibiotics product development? We cannot force companies to work in this area; rather, we must make them want to be active in this area. Before we look at incentives, we need to explore what public authorities can do already today. All medicines must be approved by regulatory agencies. At last year’s conference, there was a firm suggestion that regulatory requirements must be revised. We need comparative trials, but I think there should be rational limits set to what has to be established for the requirements of documentation. The relative effectiveness is anyhow best studied in real life. Clearly, the rules must change. And there is scope for a more step-wise approval process for much needed antibiotics.

The second hurdle is payers: pricing and reimbursement bodies that tend to compare prices against the cheapest generic. That may be appropriate for other fields, but not for antibiotics where the aim is to reward follow-on development and a multitude of products.

However, the most important thing is money: what makes small and big pharmaceutical companies hang on. I have a conviction that only private companies can develop new medicines. Financial incentives for private companies can come in many forms. Recent reviews by the London School of Economics (for the Swedish EU Presidency Conference last year) and the Institute of Medicine (for the Countermeasures Workshop) list a great number of incentives. Analyzing these, and reflecting on the dynamics of drug development and the different nature of companies, it is obvious that there has to be a multitude of changes. Some suggestions may be less likely to have success. For example, data protection or extended patents are unlikely to generate any income for products that are kept in reserve. There is no cash-flow on products kept in the drawer. What mechanisms seem most likely to really move the needle? This is a difficult question and the answer that works for one company is often not the same as for another. However, there are some ideas that seem to have the greatest plausibility at a broad level:

- A straightforward push incentive could be created via tax legislation: simple tax credit-based incentives would have the net effect of reducing the cost of development of needed antibiotics. A mechanism to carry forward such credits might be required to permit small companies without active sales to deliver this value, but that is an accounting issue that could be resolved once the principle is accepted. But I am not sure the tax route is feasible for Europe, where tax systems are a national concern. Maybe it would be easier in the US.

- One pull-based mechanism is the idea of transferable rights, i.e. when companies can extend revenue on patented blockbusters as a compensation for developing an antibiotic. Sometimes this is referred to as “vouchers”. Such an approach may be criticized by payers, but such approaches do have the intellectual advantage of spreading the costs over large groups of patients who are benefiting broadly from use of modern pharmaceuticals.

- Another possible approach is true value-based pricing, perhaps also combined with advance market commitments. Aligning prices to the value of the new antibiotic and decoupling usage from sales could be powerful tools.

- Advance purchase commitment or prizes are promising. Yet, if they are awarded only for the first product to meet certain standards, they may de-incentivize development of much-needed follow-on drugs (to combat resistance). Unlike other areas, there is a need for a rich and vibrant pipeline of follow-on antibiotics.

4. Conclusion

Most importantly, no single tool will solve the problem. What is really needed is a collection of incentives that addresses the multiple obstacles to success. For instance, and returning to the idea of the prize-based mechanism, it may be warranted to have more general milestone payments up to phase II (that means hypothesis-generations) for all compounds against a certain target, and prizes (that are paid afterwards) for successful phase III trials and registration for a limited number of products in the later phase.

Connecting the aspects I have highlighted, it is clear that incentives that separate the financial return from the use of a product are the only way to change this behavior. Intelligent pull incentives, such as advance commitments and prizes, provide financial rewards to the developer not based on the volume of use of the novel antibiotic. With the right set-up, Pharma companies will have no incentive to drive use: perhaps they will not do any promotion at all. Use would be agreed with public policy makers, purchasers and national health systems.

The mandate by the EU Council of Ministers to the Commission and the joint EU-US Task Force present two unprecedented opportunities to make a difference. The research-based pharmaceutical industry is ready to discuss and wants to be part of the solution.