

# Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales

# Executive Summary and Recommendations

---

## Introduction

Recent years have seen a resurgence of international concern about the growing problem of antimicrobial resistance, and in particular antibiotic resistance. In 2013 Chatham House's Centre on Global Health Security initiated a project to address some of the policy issues related to antibiotic resistance.

The starting point for this project was the recognition that the race with antibiotic resistance is being lost. However, while there is widespread inappropriate or excessive use of antibiotics, there are also many people who cannot afford to access antibiotics when they really need them.

There are many things that need to be done to combat resistance, including investments in water and sanitation, surveillance, infection control measures, diagnostics, vaccines and behaviour change. But because there is no way in which the development of resistance can be entirely prevented, maintaining a healthy pipeline of new products is an essential part of any solution. As part of this project, the Centre on Global Health Security convened a working group comprising representatives from academia, civil society and industry to consider how to address this issue.

Although the amounts required in one form or another to stimulate investment in research and development (R&D) are potentially large, they are very small in relation to estimates of the social value of antibiotics in terms of avoided morbidity and mortality and other beneficial health and economic impacts arising from antibiotic use. A recent estimate is that by 2050 failing to tackle antibiotic resistance could cost 10 million premature deaths per year and \$100 trillion in cumulative economic damage. This suggests that an additional global investment of up to \$3.5 billion a year (about 10 per cent of the current value of global sales of antibiotics) would be a bargain.

## The problem

Today, few large pharmaceutical companies retain active antibacterial drug discovery programmes. One reason is that it is scientifically challenging to discover new antibiotics that are active against the antibiotic-resistant bacterial species of current clinical concern. Another core issue, however, is diminishing economic incentives. Increasingly, there are calls to conserve the use of truly novel antibiotics, which might limit sales severely and discourage greater investment in R&D. Meanwhile, unless they see evidence of superiority, healthcare payers are unwilling to pay prices that would directly support the cost of development, provide a competitive return on investment

and reflect the value to society of maintaining a portfolio of antibiotics adequate to overcome growing resistance.

A principal reason for this is the mismatch between the current business model and combating resistance. The current business model requires high levels of antibiotic use in order to recover the costs of R&D. But mitigating the spread of resistance demands just the opposite: restrictions on the use of antibiotics. Economic incentives play a key role in the global resistance problem, leading to overuse of these precious drugs at the same time as companies are abandoning the field; and the increasing restrictions on inappropriate use of antibiotics make them relatively unprofitable compared with other disease areas. Other factors are also in play, including historically low prices and small market sizes.

One key policy lever for stimulating R&D while conserving antibiotic effectiveness is changing the way these drugs are paid for across the supply chain. The level of reimbursement – one incentive for firms to invest in R&D – is relatively low for antibiotics as a therapeutic class. One proposed solution is to raise prices dramatically for payers and patients, thereby incentivizing investment in R&D while also restricting use through price rationing. Even if very high prices could be engineered, however, it is not obvious that this effect on R&D would be achieved. In particular, since new antibiotics should only be used as a last resort, volumes of use may still be very low.

Moreover, even though high prices restrict demand (but in ways that are determined economically rather than clinically), they also encourage sales promotion or over-marketing. This applies not only to manufacturers but also to others in the supply chain, such as pharmacists or even doctors, whose remuneration may be linked to product value. And of course high prices exacerbate the problem that there remain many in the world who are denied access to life-saving antibiotics for economic reasons. This particularly affects patients in low- and middle-income countries (LMICs) who buy antibiotics from their own resources.

## Main findings and conclusions: the need for delinkage

New business models need to be developed in which the return on investment in R&D on antibiotics is not dependent on the volume of sales, an approach generally known as delinkage. This is because there is a need to encourage investment in R&D without also incentivizing sales volumes, which may lead to the over-marketing of antibiotics, acceleration of the development of resistance, and undermining of stewardship and conservation measures necessary to limit the growth of resistance to any new antibiotic developed.

Conservation must depend on methods of promoting appropriate antibiotic use through education, regulation and good clinical practice, rather than purely through rationing via the price mechanism unrelated to considerations of clinical need. There are many challenges involved in implementing such schemes and moving towards a business model which would need to have global reach to address a global problem.

The working group considered the issue of delinkage from a number of angles. Six of these were formulated as key questions to be answered in any successful business model for antibiotics:

- What kind of funding and incentive schemes might work?
- Which products should be covered?
- How could funding be raised?
- What is the role of intellectual property (IP)?
- How can new incentives be reconciled with rational use of antibiotics?
- How can a new scheme be applied regionally and globally?

The report considers each of these questions in turn, and the main findings and conclusions are set out below.

### **What kind of funding and incentive schemes might work?**

In considering different funding and incentive schemes, the report emphasizes that company decision-making on investing in R&D is long-term and uncertain – a decision to invest now may produce a return for a decade or more (if at all), and the market conditions are difficult to predict over that time period. Risk and reward also vary over the protracted period needed for drug development. Thus a grant provided by a government body in early-stage research is more valuable for a company, but there is a much greater risk of failure from the point of view of the funder. By contrast, a reward that is offered only after successful registration of a product is low-risk for the funder but transfers all the risk of failure to the company, so post-registration rewards need to be substantial.

There is therefore a need to create an integrated menu of incentives across the antibiotic life-cycle, including:

- Public funding of basic pre-clinical research;
- Partial public funding for clinical research, through a combination of tax credits, contracts and prizes; and
- Delinked payments after registration of qualifying products, adjusted for net public investment and as evidence of value develops.

### **Which products should be covered?**

Incentive schemes should be based on a comprehensive, periodically updated assessment of current and future global threats arising from resistance in order to identify the classes of product that are a priority for incentives. The US Centers for Disease Control and Prevention (CDC) recently carried out such an assessment for the United States. By contrast, the list of antibiotics qualifying for additional market exclusivity under the US Generating Antibiotics Incentives Now (GAIN) Act lacks any prioritization, such that most, if not all, new antibiotics would qualify.

The assessment should be data-driven, transparent and focused on the relative threats posed by resistant pathogens. The threat assessment outcome should be a triage list of pathogens, similar to the CDC classification. This threat assessment should also evaluate alternative categories (other than by pathogen) that could in some cases better target public health interventions. In this way, incentives can be directed at developing antibiotics that address unmet clinical needs.

Qualifications for support should become more stringent as the product moves towards registration. Later-stage incentives (for clinical development and post-registration) should target antibiotics that treat drug-resistant bacteria posing urgent or serious threats to humans, as determined by the evidence-based threat assessment. Pre-clinical research can target a broader range of antibiotics. Antibiotics should qualify for the highest level of new incentives if they combat resistant pathogens posing a present or predicted serious threat to human health, and such rewards should be based on demonstrably superior outcomes in human clinical testing. Antibiotics for less serious threats should qualify for a lower level of new incentives. Some flexibility should be maintained in view of inherent difficulties in predicting future health risks.

There are also questions about whether whole classes of new antibiotics (with similar mechanisms of action) should be prioritized, and how to reward follow-on innovation that adds significant therapeutic value but relates to classes that are already well populated.

### **How could funding be raised?**

There is a need to clarify exactly how much funding is required globally to tackle the different elements necessary to combat resistance – incentives for R&D, support for access and conservation, infection control and the costs of any new organizations that might be necessary. A target budget should be created, by priority goal and by unit of accountability (government, region, intergovernmental organization), for the global effort to preserve antibiotic effectiveness, based on the best evidence of clinical need and public health risk.

Consideration should be given to pooling funds on a regional or ultimately global basis, even though most funding will remain within the control of national governments. For this purpose, an international secretariat would need to be created to manage and coordinate pooled funding. Countries may be guided in their actions by agreed regional or global frameworks, coordinated through the secretariat, which would also need to identify stable sources of funding.

Various proposals have been put forward for international mechanisms to provide pooled funding for health-related actions that mainly meet the needs of LMICs. For example, the Consultative Expert Working Group of the World Health Organization (WHO) suggested that countries could commit 0.01 per cent of gross domestic product (GDP) to R&D aimed at the needs of LMICs. Others have suggested 'innovative' sources of funding such as the airline taxes that partly fund the international drug purchase facility UNITAID. In this respect, a novel feature of fighting antibiotic resistance is that the unmet needs are global – not confined to LMICs – and while finance is required for all activities, there is scope for nonfinancial contributions such as introducing effective conservation measures at relatively low cost.

Other international partnerships in science should be evaluated and could serve as models for an international initiative in antibiotics based on pooled funding. These include, for instance, the Human Genome Project, which involved multi-country participation; or the Large Hadron Collider, constructed under the auspices of CERN (the European Organization for Nuclear Research) but also including contributions from non-member states. Other financing mechanisms such as the Global Environment Facility have also been created in the environmental field.

### What is the role of intellectual property (IP)?

The delinkage business model should promote global access to antibiotics together with their appropriate use. Responsibilities should be allocated between governments and innovators when negotiating the terms of delinkage payments.

### Extensions of market exclusivity are not considered to be appropriate or effective as incentives for early-stage antibiotic development.

Post-registration delinkage rewards would be based on the principle that the companies would in return make their products available to the proposed secretariat at a price based on production costs rather than the recovery of R&D expenses. The secretariat could enter into a procurement contract with the company, acquire the full IP rights or

establish other licensing mechanisms. It would also need to set up and/or coordinate appropriate arrangements for supply and distribution and post-registration monitoring. Promoting access to new antibiotics through agreement with companies or through other mechanisms set up by the secretariat will be an important issue.

Extensions of market exclusivity are not considered to be appropriate or effective as incentives for early-stage antibiotic development. Later in the market life-cycle, the use of IP incentives to ensure monopoly pricing also risks exacerbating the over-marketing of antibiotics.

### How can new incentives be reconciled with rational use of antibiotics?

In order to reduce the use and misuse of antibiotics, significant public funds are needed to remove the causes of infection and improve the control of infections. This requires investment in clean water and in food, sanitation and vaccines, as well as in the control of infection in the community and healthcare institutions. It also requires investing in diagnostics and laboratories so that better clinical decisions can be made on antibiotic use.

In combating resistance, any new incentive system based on delinking the return on investment from the volume of sales will need to be linked to measures that will conserve existing and new antibiotics. But the availability of data on antibiotic sales and use is inadequate, particularly in LMICs.

Delinking removes a company's motivation to increase sales. On this basis, it would also be possible to engage companies in some conservation activities through appropriate incentives or contracts. Proven conservation methods such as antibiotic stewardship programmes should be incentivized and implemented immediately as part of global conservation efforts.

However, there are possible financial incentives throughout the supply chain which may lead to inappropriate or excessive antibiotic use. The WHO Global Action Plan on Antimicrobial Resistance, endorsed at the World Health Assembly in May 2015, provides a framework for action by countries to curb such use in ways adapted to their circumstances, but LMICs will require external support to intensify their conservation efforts. Some financing could be provided from funds allocated to delinkage models.

Further research is required to explore the perverse financial incentives that lead to the over- and misuse of antibiotics, and the relationship between generic entry to the market, therapeutic competition and resistance, in order to help guide the creation of mechanisms regulating entry of generic antibiotics.

Contracts with the originators of a delinked product can be used to encourage responsible use. If generic companies are involved in supply of a delinked product, this poses issues about how to regulate supply and use in the interests of conservation.

#### How can a new scheme be applied regionally and globally?

There are various ways in which a new business model could be introduced regionally and ultimately globally. Financial participation can begin with a core group of countries with significant research activity and large antibiotic markets. It is envisaged that all high-income countries should make an appropriate financial contribution; others will not be able to contribute financially at the outset, but they can contribute through surveillance, hosting clinical research, conservation and public health initiatives and national measures (e.g. on conservation, or a ban on antibiotic use as growth promoters in agriculture) that fit into an agreed global framework.

Global access to antibiotics depends on approval by national drug regulatory authorities, many of which are weak. The process of registering a product globally is costly, and leads to delays in providing access to needed antibiotics. Initiatives could be considered to develop a globally acceptable approval process that reduces these costs and delays. This could, for instance, draw on the experience of the WHO's pre-qualification programme, which approves products for use by international agencies.

The secretariat should manage the licensing of IP and secure appropriate rules for access and conservation. It should have a range of functions including coordinating IP licences, mobilizing funding for incentives, and promoting appropriate use. The Medicines Patent Pool is an existing mechanism that negotiates licences from patent holders for HIV medicines for LMICs and then sublicenses to generic manufacturers. This type of mechanism could be adapted to manage the licensing of antibiotics to generic manufacturers, using appropriate conditions to regulate access and use.

Following the adoption of the WHO Global Action Plan on Antimicrobial Resistance, countries should explore whether a treaty or a WHO regulation is the most effective way to facilitate global collective action on antibiotic resistance. There are a number of ways in which states could make stronger commitments through agreed measures aimed at promoting innovation, access and conservation. These include various instruments that could be negotiated within the WHO or through the UN General Assembly. The experience of international agreements relating to the environment or natural resources (e.g. the Montreal Protocol on Substances that Deplete the Ozone Layer) could be valuable here.

The findings of this report complement the messages of others, such as the 2014 report from the US President's Council of Advisors on Science and Technology on combating antibiotic resistance. A number of other existing initiatives, such as the European Union's Innovative Medicines Initiative DRIVE-AB project and the United Kingdom's Review on Antimicrobial Resistance, have the opportunity to investigate further the financial implications, feasibility and implementation issues of the functional elements presented for consideration here.

At the national level, the report is intended to help policy-makers consider the type of commitments, both financial and non-financial, that will contribute to an international coordinated effort to encourage development of new antibiotics, ensure access and conserve these for long-term use. Leadership from political platforms and groups of countries such as the G7, G20, OECD and BRICS is critical, both because their members constitute large antibiotic markets, and because they alone have the financial capacity to get a new business model for antibiotics off the ground. However, even smaller countries have a role to play. The Nordic Council of Ministers has suggested that the Nordic regional health cooperation should prioritize antibiotic resistance, including committing financially to incentives for innovation of new antibiotics. Similar forms of regional health cooperation in other areas of the world can provide important political leadership on antibiotic resistance.

#### Main recommendations

1. A new business model needs to be developed in which the return on investment in R&D on antibiotics is delinked from the volume of sales.
2. Increased public financing of a broad menu of incentives across the antibiotic life-cycle is required, targeted at encouraging the development of antibiotics to counter the greatest microbial threats.
3. The assessment of current and future global threats arising from resistance should be updated periodically in order to identify which classes of product are a priority for incentives.
4. The delinkage model should prioritize both access and conservation.
5. Domestic expenditures on the model need to be globally coordinated, including through the establishment of a secretariat, and global participation in the model is the ultimate goal.

---

# Independent thinking since 1920

---

The Royal Institute of International Affairs  
Chatham House  
10 St James's Square, London SW1Y 4LE  
T +44 (0)20 7957 5700 F +44 (0)20 7957 5710  
[contact@chathamhouse.org](mailto:contact@chathamhouse.org) [www.chathamhouse.org](http://www.chathamhouse.org)  
Charity Registration Number: 208223