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Antibiotic development and the changing role of the pharmaceutical industry

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1. Introduction

There is a complex relationship between the pharmaceutical industry and society. The industry, patients, physicians, regulators and politicians are all driven by their own agendas and are subject to sometimes very powerful influences [31]. The primary aims of pharmaceutical companies are, through research, development, production and marketing, to provide new medicines to improve the health of populations [24] and, as any other industry, to run a profitable business. Unfortunately, large multinational companies spend more time and financial resources on the generation and dissemination of medical information than they do on researching and developing new treatments [11,17]. Additionally, the proportion of annual revenues that these companies keep as profit is systemically larger than that invested in research and development (R&D) [42].

The pharmaceutical industry is, of course, accountable to its shareholders, but also to society at large. This latter role often seems to be forgotten by the industry, witness its inappropriate pricing of drugs, its large-scale indifference to the needs of developing countries, and the imbalance between true innovation and promotional activity [17]. Additionally, drug regulation bodies should be sufficiently robust to protect society from drugs that are unsafe, ineffective or unnecessary, but the many ways in which the industry can influence governments and regulatory agencies suggest another imbalance [1]. Clearly, the reconciliation of commercial goals and the interest of the public remains a challenge for today's society and for the industry.

The increasing number of reports about emerging multi-drug resistant bacteria and the lack of genuinely new classes of antibacterial drugs suggest that we may face the beginning of a post-antibiotic era. The unmet need for new therapies to treat bacterial infections caused by drug-resistant microorganisms should be a strong incentive to boost antibacterial R&D. However, the pharmaceutical industry is gradually deserting the field of antibiotic research and focusing its efforts on chronic diseases that require life-long daily treatment or on manifestations such as baldness or inadequate sexual performance, which have come to be considered as "diseases" deserving specific treatments [13]. Every year, many new potential antibacterial drugs are presented at scientific conferences, but very few seem to be interesting enough for the pharmaceutical industry. The problem is accentuated by large pharmaceutical companies' insisting that they need financial incentives before they can re-start their antibacterial drug development

programmes [47]. Solutions are urgently needed, and the time has come to re-think how antibacterial drugs are discovered, developed and made available for patient treatment.

2. Seventy years of antibiotic discovery, research and development by the pharmaceutical industry

Alexander Fleming, returning from his summer holidays in September 1928, discovered penicillin by looking at an agar plate where the growth of a mould, later identified as *Penicillium notatum*, had inhibited growth of staphylococci. The story of Fleming's discovery is far better known than the story of how penicillin finally ended up being produced by many pharmaceutical companies at the end of World War II. Following his first observation, Fleming cultivated the mould and obtained an active, but unstable, syrupy brown liquid from the mould juice. However, he never succeeded in completing the purification process of penicillin and a dozen years passed before a group of Oxford scientists led by Howard Florey was able to make some progress. When, on 6 September 1939, Florey made his first specific appeal for public funding to work on penicillin, he applied for £100, but received only £25. Eventually, repeated appeals for support were successful and enough money was made available for penicillin research. By the spring of 1940, the team was able to obtain a powder that was active *in vitro* and started testing it on mice. Production was carried out in the laboratory and subsequently the team struggled to produce penicillin in sufficient quantities for use in patient treatment. By May 1941, the penicillin produced at Oxford University by a team of five young laboratory technicians had enabled the drug to be tested on only six patients [37].

At the time, financial gain was not a driving force of science. According to Florey: "The people have paid for this work and they should have the benefits made freely available to them." When Ernst Chain, a member of Florey's team, argued that the drug should be patented, at least to prevent unscrupulous use, Florey took advice from two top British scientists, who confirmed that patenting of a public discovery would be considered unethical. On many occasions, Florey had presented his work to British pharmaceutical companies, but none was interested. There was also rationing in wartime Britain, and laboratory equipment and chemicals were difficult to obtain. At about the same time, the Rockefeller Foundation agreed to help him in getting a US drug company commit itself to large-scale production [37]. To promote the development of penicillin in America, the US government encouraged companies to collaborate in their work without fear of potential anti-trust violations. In 1942, Merck, Squibb, and then Pfizer, Abbott and Winthrop, were the first companies to sign an agreement to share research and production information, and include other companies that contributed to solving the problem [37].

Until the beginning of 1943, production of penicillin was still limited, but the treatment of soldiers began and by the end of the year the War Production Board (WPB) had recognised that much more penicillin had to be produced as quickly as possible. The first five companies were soon joined by 21 others, and all were given financial assistance by the WPB. By D-day, 6 June 1944, penicillin production had reached 100 billion units per month – enough to treat 40,000 patients [37].

Most other major classes of antibacterial drugs, such as cephalosporins, tetracyclines, macrolides, and quinolones, were discovered between the end of the 1940s and the early 1960s (Fig. 1). This was done mostly by screening cultures of various microorganisms for antibiotic activity. Following the discovery of a new class, R&D then focused on extending the antibacterial spectrum of existing compounds by means of semi-synthetic optimisation. One early example was the development of penicillinase-resistant penicillins in the early 1950s to treat infections caused by penicillin-resistant staphylococci that had emerged following the therapeutic use of penicillin.

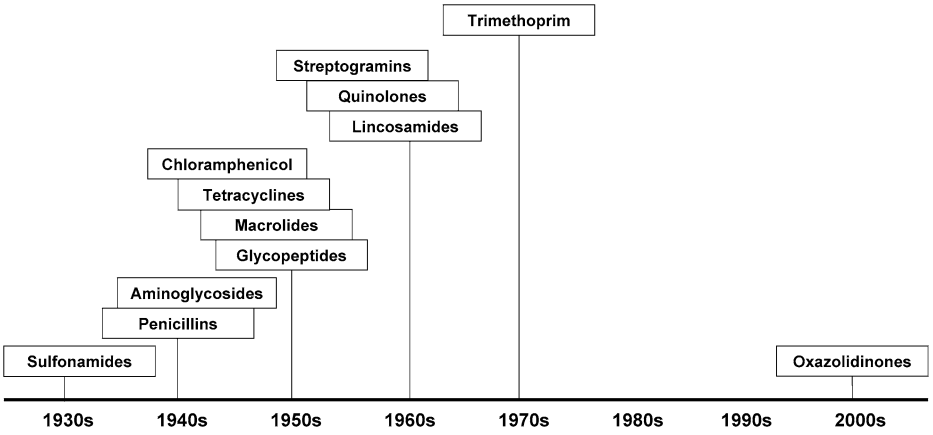

Fig. 1. Discoveries of new classes of antibacterial drugs [53].

During the 1960s and 1970s, the antibacterial drug industry emerged globally. By the early 1970s, more than 270 antibiotics had been produced [23]. More new products were introduced and profits followed. For example, by 1980, the market for third- and fourth-generation cephalosporins was increasing at the rate of nearly 30% a year [9]. In the 1980s, there were already so many antibiotics on the market that the projected profits from the development of new antibacterial drugs were seriously reduced [49]. Pharmaceutical companies started to invest in R&D of new drugs for chronic illnesses, where long-term daily treatment is often necessary; this is considered one of the major reasons for the scarcity of new antibiotics in the 1990s [49].

In 1991, approximately 50% of large pharmaceutical companies had ended, or were seriously decreasing, funding of their antibiotic research programmes because of gloomy financial prospects [50]. However, the increasing frequency of multi-resistant bacteria in some acute care settings, probably caused by the non-rational use of broad-spectrum antibiotics, had created a niche market for drugs that could overcome this resistance. This new market opportunity resulted in the development and commercialisation of several new antibiotics from the mid-1990s onwards (Table 1) [3,16,36,38,43,55,59]. Additionally, many new antibiotics are presently in the development pipeline (Table 1), and several potential new classes have recently been described, such as peptide deformylase inhibitors, bacterial RNA polymerase inhibitors, the CBR703 inhibitor series and a new ribosome inhibitor class [2,6,14,38].

Between 1993 and 2002, the number of potential agents presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) increased from approximately 90 to more than 120 [2,46] and new antibiotic targets are discovered. At ICAAC 2002, 21 companies presented targets or methods to discover new agents [2,65]. In contrast to these data, ten of the top 15 pharmaceutical companies active in 2000 have since contracted out, curtailed or ceased research on antimicrobial drugs [47,52,65].

The number of scientists involved in antimicrobial-drug discovery, both in large pharmaceutical companies and in pharmaceutical biotech companies, has dropped, which means that a whole generation of scientists specialising in antimicrobial drugs may be forced to change research area [47]. Whether through discovery of new agents, development of existing agents or in-licensing of potential agents, the efforts of those companies still interested in antibacterial drug development are now directed at finding compounds with “blockbuster” commercial potential: that is, expected annual sales of USD1 billion or more. This will certainly result in a reduction in the diversity of future antibiotics [65].

Table 1
Antibacterial drugs: Recent approvals and the development pipeline as of 2004

Status	Compound	Class
Approved	Quinupristin–dalfopristin	Synergistin (similar to macrolide)
	Linezolid	Oxazolidinone (new class)
	Moxifloxacin	Quinolone
	Gatifloxacin	Quinolone
	Cefditoren	Cephalosporin
	Ertapenem	Carbapenem
	Telithromycin	Ketolide (similar to macrolide)
	Daptomycin	Cyclic lipopeptide
In pipeline (disclosed to FDA)	Garenoxacin	Quinolone
	Cethromycin (ABT-773)	Ketolide (similar to macrolide)
	BAL-5788	Cephalosporin
	Tigecycline**	Glycylcycline (similar to tetracycline)
	PA-2794	Unknown or undisclosed
Others in pipeline (not disclosed to FDA)*	Oritavancin	Glycopeptide
	Dalbavancin	Glycopeptide
	Gemifloxacin	Quinolone
	Sitafloxacin	Quinolone
	Faropenem	Carbapenem
	Doripenem	Carbapenem
	PTK-0796	Tetracycline
	TAK-599	Cephalosporin
	CS-834	Carbapenem
	BAL-9141	Cephalosporin
	RWJ-54428	Cephalosporin
	Ramoplanin	Glycolipopeptide
	Iclaprim (AR-100)	Active on purine biosynthesis (new class)
	ECO-00501	Unknown or undisclosed

*The list is not exhaustive.
**Approved by FDA in June 2005.

3. Fewer new antibacterial drugs available for patient treatment

Although, for economic reasons, pharmaceutical companies have become increasingly interested in developing drugs for the treatment of chronic diseases, the data presented above might suggest that the antibiotic pipeline is not running dry. However, many of these new compounds do not represent true innovation, but are additions to existing classes of drug. Even the ketolides and the glycylcyclines, which are presented by pharmaceutical companies as new classes, originate from known classes. Although at present they overcome existing resistance, the risk is that resistance to these new agents will emerge faster than for a drug with a truly new mechanism of action. There are already fears that resistance to the recently approved ketolide telithromycin will quickly emerge in pneumococci [22].

The two novel glycopeptides – dalbavancin and oritavancin – have a chemical structure close to that of vancomycin. Though less toxic than vancomycin and with fewer drug interaction problems, they will certainly encounter resistance. Another problem with oritavancin is that, because of its slow elimination,

it can still be found in a patient's body 100 days after administration; this is a feature likely to foster emergence of resistance and complicate the drug's approval process by the Food & Drug Administration (FDA) [19].

In recent years, the pharmaceutical industry has generally not been very good at producing new drugs. Globally, since 1991, R&D spending has doubled, but has increased only slightly faster than revenues [26]. The number of new molecular entities approved each year by the FDA fell from 53 in 1996 to 21 in 2003 [4]. For antibacterial drugs, research has focused on the DNA sequences of microorganisms and on potential new targets. High-throughput screening of large numbers of compounds for action on DNA and biochemical targets was found more complicated, time-consuming and expensive than expected, and it did not provide the compounds that it promised [13,48]. Almost since the beginning of drug R&D, it has been easier to develop copycat compounds with no obvious clinical advantage over existing ones, but different enough to get a patent and be marketed. Because their advantage is not obvious to the prescriber or the patient, these "me-too" drugs, as Merrill Goozner dubbed them, require increased marketing efforts: "Important new drugs do not need much promotion. Me-too drugs do!" [23]. This is the case with antibacterial drugs, too.

Many large pharmaceutical companies have one fluoroquinolone in their portfolio and compete with each other for the same indications and market. In the case of carbapenems, the drugs imipenem–cilastatin and meropenem have for a long time been the only ones in this class. Since most hospitals decided to have one or the other on their formulary, thus limiting market competition, consumption has been maintained at a fairly low level and resistance is not a major problem except in particular high-user hospitals. This situation will certainly change with the expected arrival of several other carbapenems on the market.

A recent review of antibiotic patents confirms that, as for other drugs, pharmaceutical companies are still working more at modifying or combining existing antibacterial compounds than trying to find new chemical structures that could lead to new classes of antibacterial agents [43]. Indeed, the oxazolidinones represent the first new antibiotic class in 25 years (Fig. 1) – its first member, linezolid, having been licensed in 2000 [15]. As for publicly funded research, recent terrorist attacks have somewhat shifted funding priorities from a focus on emerging infectious diseases, including fighting antimicrobial-drug resistance, to the prevention of bioterrorism – the best example being Project Bioshield, a comprehensive effort on the part of the US to develop and make available modern, effective drugs and vaccines to protect citizens against potential attack by biological and chemical weapons or dangerous pathogens.

4. Who will develop and market new antibacterial drugs?

If new antibacterial agents are discovered, the remaining problem will be whether they will be developed and marketed. Because antibacterial drugs are given for short courses, they represent a small market as compared to drugs for chronic diseases that often require daily, life-long treatment. In an environment of increasing regulations and where the approval of any drug depends on demonstration of its efficacy and the way in which it will be manufactured, the risks of marketing an antibiotic are considered higher than for other drugs.

First, developing an antibiotic is potentially more difficult because the mode of action might differ from one bacterial species to another, and the new agent must be tested against all species. Second, the new antibiotic must be as effective as existing ones against susceptible strains, but must also be effective against bacterial strains that have acquired resistance to existing drugs. Third, increasing concern about

overuse and misuse among physicians and the general public has led to a general decrease in antibiotic use in several European countries and in the United States. Fourth, there is increasing pressure from health care and insurance systems to use fewer and cheaper antibiotics, and despite renewed alerts about emerging resistance, most infections are still treatable with existing antibacterial drugs [47]. Fifth, new agents specifically launched to target resistance, i.e. linezolid and quinupristin–dalfopristin, have not captured the market that they were projected to capture [47,56]. Finally, resistance to a new agent will eventually develop in connection with the commercialisation and use of any new antibacterial drug, as shown by the recent reports of linezolid resistance in methicillin-resistant *Staphylococcus aureus* [62] and vancomycin-resistant *Enterococcus faecium* [25].

The time lapse between the patenting and the commercialisation of a new drug is on average 10 years, which leaves a comparatively short period of market exclusivity before the drug may be copied by generic producers. But pharmaceutical companies want a rapid and high return on investment and have therefore turned to the development of a few potential "blockbuster" drugs, since selling large quantities of one product makes a higher profit. Very few antibacterial drugs reach the status of "blockbuster". In 2000, amoxicillin–clavulanate, with sales of USD 1.3 billion, was the only antibiotic in the list of the top 20 prescription drugs [34] and ranked 16th despite intensive marketing [29]. Its sales were about one-third those of anti-ulcerant Prilosec® and cholesterol-lowering Lipitor®, listed as number 1 and 2, respectively [34].

5. "Net Present Value" and its influence on antibacterial-drug R&D

A key parameter for the way that the pharmaceutical industry decides on priorities is the Net Present Value (NPV) of projects. This is a means of determining the value of a given project after projecting for expenses and revenues in the future and discounting for the potential investment value of investment in the project [47]. The NPV is usually risk-adjusted, most risk being associated with the earlier stages of the project. Antibacterial drugs are not especially attractive when NPV is considered. For example, Projan estimated that the risk-adjusted NPV of an injectable antibiotic targeting gram-positive bacteria was less than one-tenth of that of a particular musculoskeletal drug [47]. Oral antibiotics, which can be marketed in the community – where approximately 90% of consumption occurs – are more attractive to the industry.

According to a 2001 estimate from the Tufts University Center for the Study of Drug Development, the average cost of bringing a pharmaceutical compound through screening, chemistry, pre-clinical development and clinical testing is USD 800 million [23]. Although this figure has been cited by many, it has also been challenged. The Public Citizen/Congress Watch, for example, came up with the value of USD 71 million, using another method of calculation, adjusting for tax deductibility of R&D expenses [23]. The truth probably lies somewhere in between.

Based on an R&D cost estimate of USD 900 million, Bax observed in 2001 that, among existing antibacterial drugs, only amoxicillin–clavulanate, ciprofloxacin, clarithromycin, azithromycin and ceftriaxone, and possibly moxifloxacin, gatifloxacin and imipenem had a sufficient turnover to recoup R&D costs [9], and many of these are already facing loss of exclusivity. However, antibiotics have had the first or second shortest mean and median clinical development time in every 4-year period since 1982, mostly because of short duration of treatment and well-known endpoints for clinical trials, as well as the highest approval rate by the FDA since 1964, both of which should translate into fewer R&D expenses than for other drugs [44].

Does the biotech industry have the potential to play a leading role in antibacterial-drug R&D? According to Richard White, large pharmaceutical companies need annual sales of USD 500–800 million to recoup R&D costs [64]. For a small biotech company annual sales of USD 100–200 million, for example from an injectable antibiotic used in hospitals, may represent a substantial opportunity to recoup the investment [64]. However, the biotech companies that have prospered over the past eight years did not discover new antibiotics but were licensed to sell antibiotics discovered by others. In 1997, Cubist Pharmaceuticals was searching for alternative strategies after its antibiotic discovery programme failed and obtained a license to market daptomycin, which has recently been approved by the FDA. The compound had been discovered by Lilly in the early 1980s but its development was abandoned because of toxicity problems [10]. Even more than large pharmaceutical companies, biotech companies depend on investors, who have been very cautious because expensive investments in genomics, combinatorial chemistry and high throughput screening failed to deliver new useful compounds.

Difficulties in attracting venture capital and a more stringent economic climate forced many biotech companies to close, or at least to restructure, which often translated into a reduction in drug discovery efforts [65]. Because they lack financial stability, biotech companies are unlikely to discover new antibacterial drugs, and if they do, they will not be able to conduct development, which is more costly than the discovery phase. Because antibacterial drugs are not attractive enough for large companies, these will not obtain a license to work on a compound discovered by a smaller biotech company and carry it through the development phase.

Finally, as for neglected diseases, another solution could be to turn to non-profit drug development organisations. The Institute for One World Health, the Global Alliance for TB Drug Development, the Sequella Foundation and the Institute for Global Therapeutics are examples of such organisations that are funded by grants from governments and wealthy foundations [23]. Once the drug is developed, manufacturing rights can be transferred to a generic manufacturer, possibly in a developing country, to ensure low price and accessibility. In 2004, the WHO Department of Medicines Policy and Standards launched a project to prepare a public health-based medicines development agenda for Europe and the world [32].

6. A global, but largely unbalanced antibacterial-drug market

With annual sales at more than USD 400 billion, the pharmaceutical industry is one of the biggest and wealthiest in the world [61]. Worldwide sales of pharmaceuticals increased from USD 266 billion in 1995 to USD 341 billion in 1999 [26] and continue to increase. Despite the current weakness to the global economy, the market for pharmaceuticals is projected to grow to about USD 543 billion in 2005 [61]. A survey by IMS Health (Institute of Medical Statistics) of 13 leading markets in the period October 2002–October 2003, revealed that purchases of anti-infectives at retail pharmacies increased by 5% at a constant exchange rate and was the fifth therapeutic category behind cardiovascular, central nervous system, alimentary/metabolism and respiratory [28]. In the Far East region and in Latin America, systemic anti-infectives represent the second largest therapeutic group purchased at retail pharmacies [27] and in some low income countries in Asia and sub-Saharan Africa antibiotics represent around half of total drug expenditure. Antibacterial drugs correspond to approximately 65% of the world market in anti-infectives [60]. As in recent years, the global antibacterial-drug market, currently valued at USD 27 billion, is expected to remain basically flat, with a projected increase of only 0.6% for 2002–2008 [56]. Most antibacterial drugs are consumed by outpatients, and the hospital market, valued at USD

8 billion, represents only 30% of the antibacterial-drug market [56]. However, hospital sales are projected to increase more rapidly than sales to outpatients – that is, by 2% in 2002–2008 [56].

One global problem is that most pharmaceutical products are consumed by only a small fraction of the world's population. A projection made by IMS Health in 1999 estimated that in 2002 78% of the sales would be in North America, Europe and Japan. The other projected sales were distributed among Latin America and the Caribbean (7%), South-East Asia and China (5%), the Middle East (3%), Eastern Europe (2%), the Indian sub-continent (2%), Africa (1%), Australasia (1%) and the Commonwealth of Independent States (1%) [27]. The fastest-growing regions were expected to be North America and economically emerging regions such as the Middle East, Australasia, and South-East Asia and China, but no market analysis was reported for Africa [27]. Additionally, BUKO Pharma-Kampagne (one of the German Federal Congress of Development Action Groups) estimated that more than 40% of the medicines sold in developing countries still do not meet the basic criteria for rational medicines or, in other words, do not address the health needs of these populations [35].

In 1985, Göran Sterky wrote: "The situation is further complicated by the fact that while overuse and abuse of pharmaceuticals are common in some segments of the population in all countries, the vast majority of the people in most Third World countries, with their limited health budget and health service coverage, have little or no access to effective and safe medicines. This is so despite the fact that many Third World countries spend 30–50% of their health budgets, and sometimes more, on drugs compared to about 10% in many industrialized countries" [58]. The situation has not changed much in 2004. Twenty-five years after WHO published its first model list of essential medicines, several antibacterial drugs from WHO's list, including trimethoprim-sulfamethoxazole, trimethoprim and imipenem–cilastatin, were not on the national list of 50% or more of a panel of 17 countries [35]. Carbapenems such as imipenem–cilastatin are essential drugs for the treatment of infections due to multidrug-resistant gram-negative bacilli; however, their high price make them unaffordable to the health care systems of most developing countries. The 2001 World Trade Organization (WTO) Doha Declaration on trade-related aspects of intellectual property rights (TRIPS) mentioned that "while reiterating our commitments to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all" [35]. While the Doha Declaration has shown its effect in reducing the cost of and improving access to antiretroviral tri-therapy in some countries, there is no evidence that it had an effect on access to essential antibacterial drugs.

The problem is different with the many off-patent, older antibiotics that have legally been available in cheap, generic versions. They are widely available, but often of dubious quality. Counterfeit medicines are another global problem, which can reach enormous proportions in developing countries with negligible or no regulation [33]. In a study in Northern Myanmar, 50% of the controlled antibiotics – from China, India and Myanmar – lacked between 14% and 48% of the announced quantity of active compound, and one did not even contain the declared antibiotic [45]. In industrialised countries, the antibacterial drug market is the most crowded section of the anti-infectives market. Saturation of the market has led to polarisation between a small number of high performers and many products with lower sales. Twenty of the 41 top performing antibacterial drugs have faced or will face patent expiry between 1999 and 2010 [40]. These products facing patent expiry represent more than 50% of the total current market value and include the top 10 sellers among patented antibacterial drugs [40].

In 2000, the top 10 pharmaceutical companies worldwide spent an average 35% of their revenues on selling, general and administrative expenses – which, for a large part are for marketing – 14% on R&D and retained 19% as profits [42]. The same year, the world pharmaceutical industry reported a 6% yearly

increase in revenues and a 16% increase in profits. The median profit of the US-based pharmaceutical industry increased from about 9% in 1980 to more than 18% in 1999, while during the same time the median profit of all industries combined remained at 3–5% [12]. In 2001, as had been the case over the past few decades, pharmaceuticals ranked as the most profitable sector of US industry, with 33% profit as shareholders' equity [20]. However, companies have focused on short-term strategies such as mergers to maintain profits and the era of high profitability may come to an end. In 2003, the US-based pharmaceutical industry ranked only fourth on profits as percentage of shareholders' equity (22%) [21]. Returns to shareholders at five years fell from more than 18% for 1996–2001 to 3% for 1998–2003. It looks as though, in a few years time, the profitability of the pharmaceutical industry might not be enough for shareholders, and a new pipeline of truly innovative R&D might be needed to retain them. The wish expressed by Graham Dukes in 1985 – that the pharmaceutical industry, organised in sufficiently large units, should develop truly innovative products and be able to survive between innovations [18] – might become a necessity.

7. Possible solutions to encourage antibacterial drug development

In their review, "Perspectives on stimulating industrial R&D for neglected infectious diseases", published in 2001, Webber and Kremer divided possible solutions into two categories: push and pull mechanisms (Table 2) [63]. Push mechanisms are economic devices that aim at reducing the costs of R&D. For example, governments can encourage research in public and university labs, offer R&D tax credits (already widely used by some countries), invest public money in applied research, alone or in conjunction with private industry, e.g. the International AIDS Vaccine Initiative or the Medicines for Malaria Venture [63]. The success of the campaign against onchorcerciasis (river blindness) in West Africa shows that public-private partnership can be successful [66].

Change of legislation might be needed so that state money can be invested, as in the US National Battle Plan against Cancer or in Project Bioshield on biodefence [55]. The Infectious Diseases Society of America (IDSA) proposed a similar approach, dubbed "Bioshield II", for R&D to address drug-resistant microorganisms [30]. Sharing R&D costs between companies has also been proposed, but this presumes sharing returns and is not very attractive in the absence of improved market return.

Clinical trials for antibacterials could be made easier, shorter, and therefore cheaper, by using surrogate endpoints, better indications and labelling, and no comparator in Phase III [7,8,47,51]. However, a large part of the 60% of R&D budget spent on trials could already be saved since many trials are only designed to benefit marketing [23]. Fast-track regulatory review could sometimes be helpful, especially to small companies, but is unlikely to be sufficient to encourage more R&D [63].

Patent laws could be restructured to allow antibiotics that were previously patented but never brought to the market to have renewed patent protection [47], or to allow approval of toxic antibiotics for specific indications, for example in severely ill patients infected with multidrug-resistant microorganisms. Drugs that are admittedly toxic would not be approved under present regulations, but some have been decades ago. One example is colistin, a toxic antibacterial agent, which is now sometimes used to treat infections due to multi-resistant gram-negative bacteria [57]. Such drugs could get approval for restricted niche indications for the most severely ill patients [5].

Pull mechanisms are economic devices that address the lack of viable markets. Extension of patent term or market exclusivity on a new product is a key feature of orphan drug legislation. When the market already exists, extended patent in exchange for restricted marketing has been proposed. Mardikar

Table 2
Mechanisms to encourage industrial drug research and development [63]

Type	Mechanism	Considerations
Push	Research in public and university laboratories	Essential for basic science Less well suited to the later stages of product development
	R&D tax credits	Widely used to encourage R&D within particular region Only income-earning companies benefit
	Public investment in applied research (alone or in conjunction with private industry)	Examples include International AIDS Vaccine Initiative and Medicines for Malaria Venture Hard to pick "winners" Danger of politicisation of funding decisions Difficulty of shutting down failed programmes
	Sharing of R&D costs between companies	Sharing R&D presumes sharing returns – not attractive in absence of improved market returns Most applicable to pre-competitive research Potential antitrust difficulties
	Establishment of local development facilities (Phase III-trial support)	Usefulness varies by disease/location
	Fast-track regulatory review	Helpful, especially to small companies, but unlikely to be sufficient to encourage more R&D
Pull	Extension of patent term or market exclusivity on new product	Key feature of orphan drug legislation Market exclusivity on a product of low return is not very attractive
	Extension of patent term or market exclusivity on alternative product ("transferable patent extension")	Refers primarily to products in markets in industrialised countries Potentially very attractive to established companies but politically challenging Burden placed on patients or payers for a different medicine in industrialised-country markets (although this may be offset by subsidies)
	Tax credit on sales	Spreads the cost burden over the whole tax base Attractive to legislators Potential advantage to both purchaser and seller
	Purchase commitment, open to any firm to buy a specified product and distribute to users	Theoretically attractive, creates a market where one did not exist or was inadequate Precedents exist, albeit not in medicine Helps address price component of access problems May be best combined with increased purchases of existing products

et al. have suggested that length of patent protection should be based on sales [39]. The drug would be protected until sales have reached a total of USD 8–10 billion, this limit being reached more quickly for drugs that are widely used [39]. However, market exclusivity on a product presented as having a low return might not be attractive enough [63]. According to Projan, even wonder market exclusivity would not really help because of the rapid and high returns presently expected by the pharmaceutical industry [47].

One proposed solution is to extend patent term or market exclusivity on an alternative product, also known as "transferable patent extension" [63]. For antibacterial drugs, this would mean that, for any specific targeted indication, the company would be able to pick any drug in its portfolio and add, for example, between six months and one year of market exclusivity [47]. This solution primarily refers to products in markets in industrialised countries. It is potentially very attractive to established companies, but is politically challenging because the economic burden would be placed on patients or payers for a different medicine, possibly in another country [63].

Other solutions include tax credit on sales, which would spread the burden on the whole tax base but might encourage indiscriminate use if applied to antibacterial drugs; subsidisation of price increases to offset reduced sales volumes; and advance purchase deals to secure an incentive for investment [54]. An example of the latter can be found in vaccine history. In the summer of 1974, Mérieux made the decision to develop a vaccine to control an epidemic of type A meningitis in Brazil. Despite the absence of financial guarantee, the vaccine was rapidly developed and enough vaccine was produced to start mass vaccination in April 1975. The company finally received payment from the Brazilian government, though in instalments, during the following months [41].

These solutions are only possibilities and the question remains as to who will take the lead in antibacterial-drug R&D and put these solutions into practice. Although possibly needed, financial incentives should not be applied indiscriminately to any antibiotic coming out of R&D and should probably only be applied to truly novel compounds with a new mechanism of action. Companies should also be encouraged make the decision to limit indications of a new antibiotic to the most severely ill patients or to treat infections due to multidrug-resistant microorganisms. Through trust and commitment, a balance could be achieved between protection of innovation and access to antibacterial drugs. Only then will the pharmaceutical industry rebuild its image as a provider of new antibacterial drugs to improve the health of populations.

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