MAJOR ARTICLE

Trends in Antimicrobial Drug Development: Implications for the Future

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The need for new antimicrobial agents is greater than ever because of the emergence of multidrug resistance in common pathogens, the rapid emergence of new infections, and the potential for use of multidrug-resistant agents in bioweapons. Paradoxically, some pharmaceutical companies have indicated that they are curtailing anti-infective research programs. We evaluated the United States Food and Drug Administration (FDA) databases of approved drugs and the research and development programs of the world's largest pharmaceutical and biotechnology companies to document trends in the development of new antimicrobial agents. FDA approval of new antibacterial agents decreased by 56% over the past 20 years (1998–2002 vs. 1983–1987). Projecting future development, new antibacterial agents constitute 6 of 506 drugs disclosed in the developmental programs of the largest pharmaceutical and biotechnology companies. Despite the critical need for new antimicrobial agents, the development of these agents is declining. Solutions encouraging and facilitating the development of new antimicrobial agents are needed.

The remarkable success of antimicrobial drugs generated a misconception in the late 1960s and early 1970s that infectious diseases had been conquered. However, 40 years later, infectious diseases remain the third-leading cause of death in the United States [1] and the second-leading cause of death worldwide [2]. Furthermore, the emergence of multidrug-resistant bacteria has created a situation in which there are few or no treatment options for infections with certain microorganisms [3]. The specter of bioterrorism, which gained widespread public attention after 11 September 2001, has magnified the problem, because genetic engineering of pathogens could render them resistant to currently available antimicrobials [4–6].

Although the need for new antimicrobials is increasing, development of such agents faces significant obstacles [5, 7, 8]. Pharmaceutical research and development costs, which are estimated to be $400–$800 million per approved agent [9], pose a considerable barrier to new drug development in general. A number of factors make antimicrobial agents less economically attractive targets for development than other drug classes [10]. For example, the aging of the US population has shifted drug discovery efforts towards agents that treat chronic medical conditions that are more prevalent among elderly persons, such as hypercholesterolemia, hypertension, mood disorders, dementia, and arthritis. Conversely, antimicrobials are usually used for short-course therapies that cure disease and thus eliminate their own need in a given patient. In addition,

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the large number of antimicrobials already approved results in a high level of competition for newly developed agents. Finally, the appropriate public health need to limit use of broad-spectrum antimicrobials, thereby minimizing the pressures driving resistance, causes the medical community to discourage the first-line use of newly developed antimicrobials, negatively impacting sales [10, 11]. For these reasons, some large pharmaceutical companies have indicated that they are curtailing—or abandoning completely—anti-infective research [5, 7, 8, 10, 11]. The purpose of this study is to evaluate the impact of these research cutbacks on the availability of new antimicrobial agents.

METHODS

US Food and Drug Administration (FDA)–approved new antimicrobial agents. The number of new antibacterial agents approved from 1980 to the present was determined by searching FDA internal and online databases [12, 13]. Identical analyses were performed for new antiviral, antifungal, and antiparasitic agents approved from 1998 to the present. We defined new antimicrobial agents as "new molecular entities" (NMEs) that possess antimicrobial activity and were indicated to treat systemic infections. Topical antimicrobials, vaccines, antibodies, and immunomodulators were not considered new antimicrobial agents. NMEs were defined as chemical compounds that had not previously been approved by the FDA in any formulation. Combination agents (e.g., piperacillin-tazobactam) were only considered NMEs if $\geqslant$1 of the components had not been previously approved. Antimicrobial agents were considered to possess novel mechanisms if their molecular site of action had not been targeted by any previously approved agent.

Pharmaceutical company research and development programs. We examined the research and development programs of 15 major pharmaceutical companies and 7 major biotechnology companies via their World Wide Web listings. If a comprehensive Web listing of development programs was unavailable, we surveyed the companies' fiscal year (FY) 2002 annual reports. Products listed more than once (i.e., for multiple indications) in the development program summaries were counted only once. Drug indications (i.e., cancer, inflammation/pain, metabolic/endocrine, etc.) were independently categorized by 2 of the authors (B.S. and L.G.M.) on the basis of descriptions provided in the publicly available developmental listings. Disagreements were resolved by discussion.

The following are the 15 pharmaceutical companies whose development programs were examined: Merck & Co. [14, 15], Johnson & Johnson [16–18], Pfizer [19, 20], GlaxoSmithKline [21], Bristol-Myers Squibb [22–24], Aventis [25], Pharmacia (acquired by Pfizer after our search was performed) [26], Novartis [27], F. Hoffmann–La Roche [28–30], AstraZeneca [31, 32], Abbott Laboratories [33], Wyeth [34, 35], Eli Lilly and Co. [36–38], Schering-Plough [39, 40], and Bayer [41]. These companies represent the largest pharmaceutical companies in the world, as assessed by FY 2001 revenues [42–44]. Bayer derives only a portion of its revenues from pharmaceutical sales. Nevertheless, because it is the maker of the antimicrobials ciprofloxacin and moxifloxacin, for the purposes of this study it was considered a pharmaceutical company (by 2001 revenues, the fifth largest in the world) [42–44].

Of the world's 10 largest biotechnology companies [45], the following are the 7 whose development programs were examined: Amgen [46], Genentech [47], Applera [48], Genzyme [49], Serono [50], Chiron [51], and Biogen [52]. We did not examine the developmental programs of the remaining 3 biotechnology companies because 1 of them (Immunex Corporation) had recently been acquired by Amgen, and because 2 of them (Amersham Biosciences and Invitrogen) do not produce therapeutic products.

RESULTS

FDA approval of new antimicrobial agents during 1983–2002. The number of newly approved antibacterial agents decreased during the 20-year period from 1983 to 2002 (figure 1). From 1998 to 2002, FDA approval of new antibacterial agents decreased by 56%, compared with the period from 1983 to 1987. Of 225 total NMEs approved by the FDA from January 1998 through December 2002, seven (3%) were for new antibacterial agents (table 1). No new antibacterial agents were approved in 2002. On 7 April and 12 September of 2003, gemifloxacin and daptomycin were approved, respectively. Of the 9 new antibacterial agents approved since January 1998, two

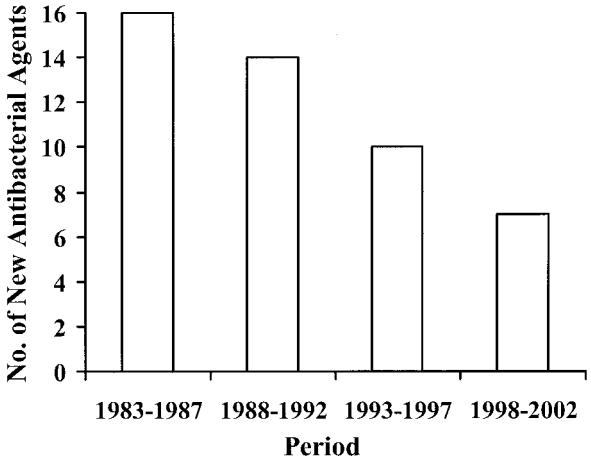

Figure 1. New antibacterial agents approved in the United States, 1983–2002, per 5-year period.

Table 1. New antibacterial agents approved since 1998.

Drug	Year approved	Novel mechanism
Rifapentine	1998	No
Quinupristin/dalfopristin	1999	No[a]
Moxifloxacin	1999	No
Gatifloxacin	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin	2003	No
Daptomycin	2003	Yes

[a] The mechanism of the streptogramins (quinupristin and dalfopristin) is closely related to that of the macrolide/lincosamide families [63].

(linezolid, which was approved on 18 April 2000, and daptomycin) have novel mechanisms of action (table 1).

Two new antifungal agents (caspofungin and voriconazole) and 2 new antiparasitic agents (atovaquone/proguanil and nitazoxanide) have been approved since January 1998. In comparison, 9 new antiviral agents were approved from 1998 through 2002, five of which were HIV-specific agents. In March, June, July, and October of 2003, the FDA approved additional anti-HIV agents (enfuvirtide, atazanavir, emtricitabine, and fosamprenavir, respectively). Thus, from January 1998 through December 2003, as many drugs were approved for the treatment of HIV ($n = 9$) as for the treatment of all bacterial infections ($n = 9$).

Antimicrobial agents in current pharmaceutical developmental programs. Given the time required to bring a molecule "from the bench to the bedside" [5], FDA databases of approved drugs generally reflect pharmaceutical research and development activities over the decade preceding approval. To project the potential for the development of novel antibacterial agents over the coming decade, we surveyed the research and development programs of the world's 15 largest pharmaceutical companies. Of note, these companies were responsible for developing 93% of the 57 new antibacterial agents approved by the FDA from January 1980 to December 2003.

A total of 418 agents, of which 315 are NMEs, are listed in publicly disclosed descriptions of these companies' research and development programs (table 2). Thirty-one (10%) of these NMEs are categorized as anti-infectives, of which 5 (1.6%) are new antibacterial agents (table 3). None of these agents appear to possess novel mechanisms of action (table 4). In contrast, there are 17 antiviral NMEs (5.4%) listed in these research and development programs (table 3), 12 of which are HIV-specific agents (4 of which, as mentioned, were approved by the FDA in 2003). Six of the 12 anti-HIV agents possess novel mechanisms of action (2 are integrase inhibitors, 2 are fusion inhibitors, 1 is an CCR5 antagonist, and 1 is an "entry inhibitor"). Thus, there are more than twice as many anti-HIV drugs as antibacterial agents in development, and one-half of the HIV-specific agents possess entirely novel mechanisms of action, compared with none identified for the antibacterial agents.

Finally, in comparison with antibacterial agents, numerous NMEs are listed in development for various diseases that are not as immediately life-threatening as serious bacterial infections (table 5).

Pharmaceutical research and development expenditures. To confirm that the decrease in antibacterial drug development did not reflect an overall decrease in research and development activity, we reviewed the research and development expenditures disclosed in the FY 2002 and FY 1998 annual reports of the following 10 pharmaceutical companies: Merck & Co. [14, 15], Pfizer [19, 20], Bristol-Myers Squibb [22–24], Abbott Laboratories [33], AstraZeneca [31, 32], Eli Lilly and Co. [36–38], F. Hoffman–La Roche [28–30], Johnson & Johnson [16–18], Wyeth [34, 35], and Schering-Plough [39, 40]. These 10 companies were chosen because their annual reports, which are available online, listed research and development expenditures for both FY 2002 and FY 1998, and expenditures were reported in US dollars. In FY 1998, the total research and development expenditures for these 10 companies were $21.9 billion in 2002 adjusted dollars, whereas, in FY 2002, research and development expenditures totaled $28.6 billion. Therefore, overall research and development expenditures increased 31% during the 5-year period, even while antibacterial drug development was curtailed.

Table 2. New molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies.

Indication or type of agent	No. of NMEs
Cancer	67
Inflammation/pain	33
Metabolic/endocrine	34
Pulmonary	32
Anti-infective	31
Neurological	24
Vaccines (passive or active)	18
Psychiatric	16
Cardiac	15
Hematologic	12
Gastrointestinal	13
Genitourinary	12
Ocular	4
Dermatological	4

Table 3. Anti-infective new molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies.

Type of agent	No. of NMEs
Anti-HIV	12
Other antiviral	5
Antibacterials	5
Antiparasitics	5
Antifungals	3
Topical	1

Antimicrobial agents in current biotechnology developmental programs. To determine whether biotechnology companies are filling the gap in antibacterial development, we examined the development programs of the world's 7 largest biotechnology companies. Of a total of 88 drugs that have been publicly disclosed to be in development by these companies, 81 are NMEs, and 1 (1.1%) is a new antibacterial agent (table 6).

DISCUSSION

Given an average of 8 years required to bring a drug from phase I clinical testing to product launch [5], the diminishing number of approvals of new antibacterial agents since 1998 is a "trailing-edge" marker, indicating that the decline in antibacterial research and development is $\geqslant$1 decade old. Even more concerning is that no reversal in this trend is apparent for the foreseeable future. Although telithromycin is currently under FDA review, it is unclear how many of the 4 other agents disclosed in development by the world's largest pharmaceutical companies will ultimately receive approval. As well, none of these agents appear to possess entirely novel mechanisms of action.

The development of new drugs within an existing class is advantageous in that it can lead to improved safety profiles, more advantageous dosing schedules, and the acquisition of data for diseases or populations previously unstudied for that class. The development of new drugs within an existing class may also provide incremental improvement in antimicrobial spectrum (e.g., cefazolin vs. ceftriaxone vs. cefepime). However, only the development of new classes of antimicrobials with novel mechanisms of action can fully address the burgeoning drug resistance in common pathogens and the theoretical concern of genetically engineered, multidrug-resistant agents in bioweapons [4–6]. This need for novel classes of antimicrobials was emphasized in a recent report by the National Academy of Science's Institute of Medicine, which stated that, "The absence of new classes in the [pharmaceutical] pipeline … is alarming when one considers the ever-increasing numbers of antibiotic-resistant organisms" [5, p. 191].

Smaller companies, as exemplified by the biotechnology industry, may be more likely to develop a drug with a smaller market—and, therefore, a smaller profit margin—than are larger companies. However, given the potentially concerning economic trends facing the biotechnology industry [53], it is unclear whether biotechnology companies can fill the gap in anti-infective research and development created by the withdrawal of many large pharmaceutical companies from this field. Indeed, only 1 new antibacterial agent is disclosed in the development programs of the world's largest biotechnology companies.

Other small pharmaceutical or biotechnology companies are developing new antibacterial agents not reflected in this dataset (e.g., a cephalosporin in phase I testing and "lipopeptides" in preclinical testing by Cubist Pharmaceutical [54], oritavancin in phase III testing by InterMune [55], and dalbavancin in phase III testing by Vicuron Pharmaceuticals [56]). However, despite these and other promising agents in development by smaller biotechnology companies, in the past, large pharmaceutical companies have been more likely to bring a product to market than smaller companies. Although Cubist Pharmaceutical ultimately brought daptomycin to market, the drug

Table 4. New antibacterial agents publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies and 7 largest biotechnology companies.

Company	Product	Novel mechanism
Pharmaceutical companies		
Bristol-Myers Squibb	Garenoxacin	No (fluoroquinolone)
Aventis	Telithromycin	No (ketolide)[a]
Abbott	ABT-773	No (ketolide)[a]
Hoffman–LaRoche	BAL5788	No (cephalosporin)
Wyeth	Tigecycline	No (glycylcycline)[a]
Biotechnology companies: Chiron	PA-2794	Unknown

[a] Ketolides and glycylcyclines are modified macrolides and tetracyclines, respectively.

Table 5. Selected new molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies.

Indication or type of agent	No. of NMEs
Depression	14
Anxiety	9
Bladder hyperactivity	8
Osteoporosis	7
Antibacterials	5
Erectile dysfunction	4
Obesity	3

was discovered and developed in the 1980s and early 1990s by Lilly Research Laboratories [57]—one of the largest pharmaceutical companies in the world—and was in-licensed by Cubist Pharmaceutical in 1997 [54]. Similarly, gemifloxacin was in-licensed for marketing by Genesoft, but it was developed and studied by Glaxo-SmithKline, a large pharmaceutical company. Although small companies have brought these drugs to market, this still does not address the need for new drug discovery. Indeed, from 1980 through 2003, large pharmaceutical companies developed 93% of the new antibacterial agents approved by the FDA. Therefore, projecting a decade into the future, it appears likely that the diminished availability of new antibacterial agents will worsen.

There are limitations of the datasets used in this study. Small pharmaceutical and biotechnology companies were not surveyed because the lack of an auditable reference for selecting which companies to survey would have increased the likelihood of inducing a selection bias regarding which companies to include in the survey. Furthermore, as stated, historically large companies have discovered and developed the majority of available antibiotics. For these reasons, a publicly available list of the largest companies was used to allow an objective mechanism for determining which companies to survey.

We emphasized antibacterial agents because bacteria are by far the most common cause of infection-related deaths in the United States [1]. Furthermore, consideration of new antifungal and antiparasitic agents does not alter our conclusions. Antiviral medications were considered separately because factors in the decisions to develop HIV drugs are different than factors involved in the decisions for antibacterials (see below). Vaccines and immunotherapies were not included in the analysis because the barriers and incentives for development of both passive and active immunization, as well as cytokine modulation, differ considerably from those for development of small molecules designed to treat active infections.

We recognize that pharmaceutical companies do not publicly disclose all products in their development programs. There is marked variation from company to company in the extent to which such research and development program lists are made available to the public. Nevertheless, pharmaceutical companies are equally likely to publicly disclose development of antibacterial agents as any other class of drugs; thus, there is likely to be no bias against inclusion of antibacterial agents in pharmaceutical drug development lists. Despite discussions with the FDA and pharmaceutical representatives, we are unaware of any other publicly available databases that more thoroughly list products in development by pharmaceutical and biotechnology companies. Other search strategies, such as enumeration of novel compounds listed in abstract presentations at scientific meetings, are more likely to identify early phase compounds that are not mature enough to be listed in publicly disclosed records. However, such a mechanism is likely to overestimate the probability of future clinical drug development, because the attrition rate of preclinical phase compounds is high. Furthermore, without a comparator value from prior decades, such a mechanism would also be unlikely to shed light on the current trend in drug development compared with that in prior years.

In spite of the limitations of this study, it is clear that current antimicrobial drug development is insufficient to meet society's needs. Physicians are increasingly confronted by common infections now responsive to a single agent or even to no antimicrobials at all. Widespread resistance to antimicrobial agents affects all medical specialties, not just infectious disease specialists or hospitalists. For example, the increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* [58–60] infections limits the use of an oral penicillin or cephalosporin for complicated skin and soft-tissue infections. *Streptococcus pneumonia,* the most common cause of community-acquired pneumonia, is increasingly resistant to penicillins, macrolides, and fluoroquinolones [61–64]. Furthermore, the emergence of vancomycin resistant *S. aureus* [65,

Table 6. New molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 7 largest biotechnology companies.

Indication or type of agent	No. of NMEs
Inflammation/immunodulator	24
Metabolic/endocrine	15
Cancer	13
Inherited enzyme deficiencies	9
Cardiovascular condition	6
Hematologic condition	3
Dermatologic condition	3
Renal condition	3
Neurology	2
COPD/asthma	2
Antibacterial agent	1

NOTE. COPD, chronic obstructive pulmonary disease.

66], linezolid-resistant *S. aureus* [67] and *Enterococcus* [68, 69], and multidrug-resistant gram-negative rods [70–74] may result in limited treatment options for skin, urine, and systemic infections that were formerly readily curable with commonly used antimicrobials. Globally, multidrug-resistant tuberculosis has become an increasing problem requiring the use of older treatments associated with greater morbidity, such as therapeutic pneumothoraces [75–77]. Finally, the threat of a bioterrorist attack with multidrug-resistant anthrax, plague, or tularemia is a widely discussed public health concern [4, 5]. The solution to these problems is to establish a continuum of development of novel antibacterial agents [5].

Certain economic barriers to antibacterial development are less problematic in anti-HIV research and development. For example, patients infected with HIV take medications for life. Therefore, HIV infection, unlike bacterial infections, fits well with the current research and development trend emphasizing chronic diseases. Furthermore, although there is some competition in the HIV market, with a substantial number of currently approved HIV medications (20, including the 4 approved in 2003), considerably more competition exists in the antibacterial market, in which there are ⩾90 agents available [78]. The result of these and other differences is more robust sales for new HIV medications than for new antibacterial agents [10]. The laudable, continuing success of anti-HIV drug development indicates that anti-infective research remains attractive to pharmaceutical companies when barriers to drug development are diminished. However, the problems of antibacterial autoobsolescence, significant competition in the antibacterial market, and the need to limit the use of broad-spectrum antibacterial agents to prevent emergence of resistance will not dissipate of their own accord.

To encourage a continuum of development of antimicrobial drugs, a thorough and comprehensive analysis is needed to create solutions to overcome these barriers. Recently, a similar analysis for anticancer agents led to the development of legislation by the US Congress intended to "increase cancer research and speed the discovery and application of new cancer treatments to find cures" [79]. Among the mechanisms proposed to spur cancer research are an increase in funding of the National Cancer Institute, creation of $120 million in annual grant programs to spur research in cancer drug discovery and development, salary and loan support for physicians and scientists who commit to spend 3 years as cancer researchers, and expansion of the orphan drug program. The drafting of legislation to spur the development of anticancer agents underscores the need for similar efforts to improve anti-infective research and development. Such efforts may include the following: (1) the exploration of combined programs for antibacterial drug research and development involving the National Institutes of Health (NIH), academia, and industry; (2) continuing efforts to streamline the drug approval process when feasible, without compromising safety and efficacy standards; (3) the possibility of government contracts with industry to develop antibacterials to meet specific national needs; and (4) introduction and passage of legislation to provide economic incentives for industry, such as those under consideration for antibioterrorism agents within Project Bioshield and for anticancer agents in the National Battle Plan Against Cancer [79].

The withdrawal of the pharmaceutical industry from antimicrobial drug development is a societal problem with potentially serious public health consequences. To begin addressing this problem, the FDA has sponsored 2 meetings between the Infectious Disease Society of America, the NIH, the FDA, and the Pharmaceutical Research and Manufacturer's of America [7]. The discussions in both meetings have considered selected aspects of the crisis and have been successful in initiating more formal preliminary responses to this critically important issue. However, given the increasing antimicrobial resistance in common pathogens, and the potentially catastrophic consequences of a bioterrorist attack with multidrug-resistant pathogens, far more robust activity is pivotal to creating innovative solutions that will remove current barriers to new antimicrobial drug development.

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Note added in proof. Telithromycin received FDA approval on 1 April 2004.