PROMOTING ANTIBIOTIC DISCOVERY AND DEVELOPMENT
A CALIFORNIA HEALTHCARE INSTITUTE INITIATIVE
Executive Summary

Successful treatment of bacterial infectious diseases requires the availability of effective antibiotics. Since their earliest discovery, the global use of antibiotics agents has improved the quality and length of life for countless people. Antibiotics were unquestionably one of the major medical advances of the last century and it is fair to say that much of modern medicine is predicated on their availability. They are crucial in the treatment of infections, which occur following major trauma or in patients in intensive care. They also play an important role in the prevention of infection following surgery or in the treatment of life-threatening infection in patients with cancer or leukemia. The widespread use of antibiotics has a downside, however, owing to the predictable emergence of antibiotic-resistant organisms. Even though this phenomenon can be blunted when the agents are used judiciously, appropriate use does not preclude the development of antibiotic resistance completely. As bacterial pathogens mutate, continued success in treating infectious diseases requires a steady stream of new antibiotics to which existing bacteria have not developed resistance.

Drug-resistant infections and related morbidity and mortality are on the rise in the United States and around the world. The Centers for Disease Control (CDC) has defined antimicrobial resistance as a major public health issue, and the World Health Organization (WHO) has identified it as one of the three greatest threats to human health. The Department of Homeland Security also recognizes pan-resistant microbes as a national security threat.

Not only is antibiotic resistance on the rise, but emerging pathogens are seen in ever-growing populations. Newly identified pathogens are resistant to a broader panel of drugs and sometimes to entire classes of antibiotic agents. Previously thought limited to hospitalized or nursing home patients, outbreaks occur regularly in otherwise healthy populations. Some emerging pathogens are highly resistant to the entire library of known antibiotics.

While the need for effective new antibiotics is clear, the drug development pipeline has not kept pace. Major pharmaceutical companies have largely abandoned the antibiotic space because the path to market and profitability is uncertain. In order to encourage industry to re-engage with antibiotic drug discovery, clinical, regulatory, marketplace, economic, and stewardship challenges must be addressed. In large part, the U.S. Food and Drug Administration (FDA) has the power and the ability to solve this problem. This is because the most important barrier to industry investment is the FDA regulatory process. But this process is flexible and can adapt to public health crises. During the early 1990s, for example, the FDA worked with industry on new classes of drugs that eventually changed HIV/AIDS from a death sentence to a manageable chronic disease. It has also sped up the approval process for new and effective treatments for hepatitis C. More recently, the agency has demonstrated efficiency in approving new oncology products. Given the importance of developing novel antibiotic, anti-infective and anti-fungal drugs, we encourage the FDA to reconsider its regulatory pathway and to construct a system that attracts investment on a scale that matches the growing threat to public health.
I. Background

In 1900, the three leading causes of death in the United States were pneumonia, tuberculosis, and enteritis — all infectious diseases. A century later, heart disease, cancer, and stroke — all chronic, non-infectious diseases — had replaced these at the top of the list. The shift in leading causes of death from infectious to chronic diseases is partly credited with raising average life expectancy by over 30 years. Much of this increase has been attributed to massive reductions in infectious disease mortality, which disproportionately impacts the young. These shifts have come to be known as an “epidemiologic transition,” perhaps the most notable achievement in the modern history of public health. Antimicrobial drug development became a transformative moment in human history, beginning with Sir Alexander Fleming’s penicillin discovery in 1928. Antibiotics were quickly recognized as wonder drugs, as “magic bullets,” and the possibilities they offered seemed infinite.

Over the ensuing 70 years, the subsequent development of a multitude of anti-infective agents and measures has largely been responsible for increased life expectancy in developed countries beyond 80 years, and for the elderly accounting for more than 15 percent of the population. Today, leading causes of death are far more likely to be due to chronic conditions such as heart disease and cancer than infectious disease (Yoshikawa 2002).

Leading physicians who have borne witness to the changes occurring in medicine have described these discoveries as “an awesome acquisition of power” for physicians and their patients. After decades of impressive success against a range of infectious diseases previously viewed as fatal, medicine considered the problem solved. Reflecting the sentiment at the time, U.S. Surgeon General William H. Stewart is said to have declared that it was “time to close the book on infectious diseases and declare the war against pestilence won.” (Spellberg et al. 2008).

Despite the positive impact the discovery and development of antibiotics had on treating infectious diseases, their widespread use accelerated the emergence of microbial resistance, weakening their effectiveness in treating ever-evolving pathogens. This resistance was recognized, but poorly understood. The pipeline of new and effective agents seemed endless. But attempts to use these agents judiciously were inconsistent. As soon as resistance to one agent emerged, newer, more effective drugs were introduced.

Unfortunately, the widespread use of antibiotics — in animal feed and in treating human disorders — has accelerated the predictable emergence of microbial resistance, and it has weakened their effectiveness in treating disease. Microbial resistance to antibiotics challenges the notion that the “war” is over, or that it was ever “winnable.”

The inevitable development of resistance by microbes means that a steady stream of new drugs needs to be discovered and developed if we are to sustain our ability to treat infections. The treatment of gonorrhea is a case in point. Penicillin was given to GIs on leave during the Korean War to treat gonorrhea. All this did was lead to penicillin resistance, which has persisted to this day; just recently this bacterium, Neisseria gonorrhea, has become resistant to the last available oral agent; now the only treatment is a painful intramuscular injection.

When a physician prescribes an antibiotic to treat an infection, he or she will select the specific antibiotic and dose that are most likely to cure the disease. If the wrong antibiotic is chosen or the dose is too low to treat the disease, some bacteria — those most resistant to the drug used — will survive and reproduce, allowing the disease to return or prolonging the resolution of the infection. Unfortunately, just as anti-microbial resistance is increasing, the production of new FDA-approved antibacterials has decreased precipitously over the past 25 years, and the number of antibacterials in clinical development remains disappointingly small. Indeed, antibiotic approvals by the FDA from 1983 through 2007 declined by 75 percent, with evidence of continued decrease in approvals, even during the most recent five-year period (Boucher et al. 2009).

Success in treating microbial resistance to antibiotics requires that new drugs provide clear advances in treatment of infection, compared with available therapies. In addition to the paucity of new antibiotics being in the development pipeline, the number of truly novel compounds with a new mechanism of action is even smaller. Most antibacterial drugs that are currently in the late-stage pipeline do not promise a major advance in our ability to treat infection, due to resistant pathogens.

Major pharmaceutical companies have limited their development efforts in the antibiotic research space. In an analysis of trends in pharmaceutical discovery and development, bacterial disease trials differed from almost every other disease system studied in
showing a decrease in the number of trials between 2005 and 2007. In addition, the proportion of early-phase trials in this area showed an even greater decline, thus underlining the diminishing industry focus on antibacterials in the past decade (Karlberg 2008).

Antibiotics are different from most drugs in a pharmaceutical company’s portfolio. They are usually prescribed for short, defined periods of time, and they are intended to cure the condition for which they are prescribed. For these reasons, antibiotics are victims of their own success — they are less attractive to drug companies and venture capitalists, in part, because they are more successful than other drugs at treating and curing. Moreover, the typical development of resistance assures their eventual obsolescence, often long before expiration of patent protection. Concerns about over-prescription of antibiotics, aggravating the problem of resistance, place additional limits on the market. Such factors make the antibiotic development space unique, and ensure that it operates differently from conventional economic models in the pharmaceutical industry, where blockbuster drugs used to treat chronic conditions in large populations have held sway in recent years. While there is a trend toward developing new business models — personalized medicine, for example — drug manufacturers have found it difficult to balance their cost and pricing structures to reflect the full value of innovative products. Because of current regulatory and market incentives, blockbusters remain sources of greatest profit. The application of this current paradigm to antibiotic development ignores the inherent differences between antibiotics and all other classes of drugs, and assures the inequitable competition for finite research and development (R&D) resources within pharmaceutical companies. In the new era of personalized medicine and genomics, the pharmaceutical business model is moving away from reliance on blockbuster drugs. With respect to antibiotics and anti-infective products, industry and governments must work together to develop new business models that encourage adequate investment in their development.

Market models have been implemented successfully for the treatment of chronic viral illnesses such as HIV and hepatitis C (HCV). Especially when combined with a favorable regulatory climate, the chronic model has been extremely successful in bringing new life-saving therapies to market. A hybrid model of central government-based incentives and policies, combined with free-market economics, also has worked well in developing many new and successful vaccines. What is clear in all of these successful cases is that the FDA is a key player. If the FDA rightly perceives an unmet medical need then it can and does successfully adjust the approval process to ensure the introduction of safe and effective life-saving drugs which are sorely needed. If the FDA does not perceive an unmet medical need nothing will happen and patients will suffer. The successful establishment of a sustainable R&D infrastructure will require incentives that reduce the regulatory barriers and development costs along with those that will assure eventual marketplace success and an adequate return on investment. The key component is a streamlined regulatory and approval process in which the FDA facilitates the introduction of new safe and effective antibiotics. The widespread and growing problem of multidrug-resistant infections ignores borders and is on the verge of being of epidemic proportions. The re-establishment of antibiotic development as a viable option for investors in pharmaceuticals is imperative for our continued safety and health.

II. Burden of Bacterial Infections
a. Problematic pathogens

The Infectious Diseases Society of America (IDSA) created a list of high-priority bacterial and fungal pathogens for which there were few, if any, treatment choices available or in clinical development in 2006 (Talbot et al. 2006). As increasingly resistant organisms continued to emerge, the Society has identified six pathogens as particular threats, as they cause the majority of nosocomial infections. In 2008, these pathogens have become known as the ESKAPE bacteria — *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter species* (Boucher et al. 2009, Rice 2008). The increasing global threat of multi-drug resistant Mycobacterium tuberculosis (TB) is usually included as a member of this family of increasingly resistant bacteria. Finally, because of the increasing number of patients
with suppressed immune systems as a result of other medical treatments, such as chemotherapy or organ transplant rejection therapy, fungal infections resistant to medications are emerging as an increasing problem with risk to larger populations.

**i. Methicillin-resistant *Staphylococcus aureus* (MRSA)**

MRSA is a Methicillin-resistant *Staphylococcus aureus* bacteria. This micro-organism is known for causing skin infections, in addition to many other types of ailments. There are other designations in the scientific literature for these bacteria according to where the bacteria are acquired by patients, such as community-acquired MRSA (CA-MRSA), and hospital-acquired MRSA or epidemic MRSA (EMRSA).

Staph MRSA-related hospitalizations have increased 119 percent, according to the Centers for Disease Control and Prevention. From 1999 to 2005, MRSA-related hospitalizations more than doubled, growing from 127,036 to 278,203 and the number of hospitalizations involving *S. aureus*-related infections also increased from 294,570 to 477,927. In 2003, the European Antibiotic Resistance Surveillance System (EARSS) defined MRSA as a growing threat, accounting for more than 25 percent of *Staphylococcus* isolates in nine of its member nations:

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#### Annual death rates in the United States for selected infectious diseases

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>No. of deaths (estimated)</th>
<th>Year</th>
<th>Reference</th>
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<tr>
<td>MRSA infection</td>
<td>19,000&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2005</td>
<td>[14]</td>
</tr>
<tr>
<td>AIDS</td>
<td>15,798</td>
<td>2004</td>
<td>[15]</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>662</td>
<td>2004</td>
<td>[16]</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>5793</td>
<td>2002</td>
<td>[17]</td>
</tr>
<tr>
<td>SARS</td>
<td>0</td>
<td>All</td>
<td>[18]</td>
</tr>
<tr>
<td>Avian influenza</td>
<td>0</td>
<td>All</td>
<td>[19]</td>
</tr>
</tbody>
</table>

<sup>a</sup> In-hospital deaths

*NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*, SARS, severe acute respiratory syndrome.*

Source: Boucher and Corey 2008
ii. Vancomycin-resistant *Enterococcus* (VRE), fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP)

Although MRSA represents the greatest overall problem at present, several more pathogens are not far behind in terms of incidence and morbidity. Vancomycin-resistant *enterococcus* (VRE) and fluoroquinolone-resistant *Pseudomonas* (FQRP) show similar rates of emerging resistance patterns, and are proving to be extraordinarily difficult problems in many hospitals across the United States:
iii. *Klebsiella pneumonia, Acinetobacter baumanii, Pseudomonas aeruginosa, Eschericia coli*

Perhaps even more alarming is the emergence of bacteria highly resistant to all antibiotic agents. The increasing incidence of pan-resistant gram-negative pathogens — most notably Klebsiella, Acinetobacter, Pseudomonas, and Escherichia coli species — have been responsible for notable yet limited epidemics in the United States and around the world. Resistance to carbapenems (an antibiotic class that is considered as the last line of defense against these species) is now observed increasingly worldwide, and constitutes a sentinel event for emerging antimicrobial resistance. Resistance against carbapenems is considered, in and of itself, sufficient to define an isolate as highly resistant. Such resistance was largely unknown in the United States less than 10 years ago but has now been identified throughout most of the country.
These resistant Klebsiella strains are seen in even more striking fashion in Europe, where more than 50 percent of isolates are resistant to carbapenems:

Bacteria grow through cellular division, which results in the production of two daughter cells genetically identical to the parent cell. When resistance to an antibiotic develops in one cell, this resistance is then passed on to all subsequent members of a particular cell line. This is known as vertical transmission of resistance. Although not common, drug resistance can also be spread by bacteriophages. Viruses that infect bacteria are called phages. These sub-cellular fragments can transform a harmless ancestral bacterial strain into a lethal pathogen. Bacteria, however, have evolved a more common and more efficient means of microbial resistance by conjugal transfer of plasmids to other bacteria of the same or different species. This is known as horizontal transmission of resistance.

One of the most dreaded forms of antibiotic resistance currently known is the New Delhi metallo-beta-lactamase-1 (NDM-1), in which a gene encoding an enzyme to deactivate antibiotics can be transferred from one species of bacteria to another. Since its initial identification in the city which bears its name, this self-propagating vector has spread rapidly and has been seen in all of the gram-negative ESKAPE bacteria throughout much of the world:
Mycobacterium tuberculosis

Tuberculosis has been present in humans since antiquity. Tuberculosis caused the most widespread public concern in the 19th and early 20th centuries as an endemic disease. In 1815, it caused one in four deaths in England; by 1918 one in six deaths in France were still caused by TB. It was not until 1946 with the development of the antibiotic streptomycin that effective treatment and cure became possible. Prior to the introduction of this drug, the only treatments besides sanatoria were surgical interventions which provided little or no benefit.

During the mid-20th century it seemed reasonable to hope that TB could be eradicated. But these hopes were dashed with the rise of drug-resistant strains in the 1980s. For example, tuberculosis cases in Britain, numbering around 50,000 in 1955, had fallen to around 5,500 in 1987, but in 2000 there were over 7,000 confirmed cases. Although only about 10 percent of infected people develop overt signs of the disease, about one-third of the world’s population is thought to harbor the TB bacterium, and new infections occur at a rate of about one per second. The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing. In 2007, there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths.

The resurgence of tuberculosis and its increasing resistance to antibiotic therapy resulted in the declaration of a global health emergency by the World Health Organization in 1993.
Ironically enough, TB is a byproduct of modern technology. The increasing availability and duration of air travel, and the rising numbers of travelers has expanded the potential exposure to people with infectious TB. Because TB is an airborne disease, the long periods of confinement in close proximity to large numbers of people who may not even know they are infected has led to the transmission of infection.

**vi. Fungal infections**

In contrast to the risk posed by multi-drug resistant bacteria, which cause increasing numbers of infections in previously healthy patients, fungal infections occur most often when a patient has a predisposing decrease in their body's immunity to infection. Cancer patients treated with chemotherapy, organ transplantation recipients receiving immune suppressant medications, patients in the intensive care units (ICUs) of hospitals, and patients living with HIV have become part of the fabric of our society. All of these groups represent growing populations of patients particularly susceptible to fungal infections. Although not as frequent as bacterial infections (fungal infections account for about 10 percent of bloodstream infections in hospitalized patients), they tend to represent a greater threat—about 40 percent of fungal bloodstream infections prove fatal. This percentage approaches 50 percent for those patients in an ICU setting. (Wisplinghoff H CID 2004)

Fungi differ from bacteria in some very important ways. Fungi tend to grow slower than bacteria; successful eradication of the disease often requires a more prolonged course of treatment. Of further concern is the lag in the ability to diagnose a fungal infection (Alexander B Transplant Infect Dis 2002)

Fungi develop in parts of the body less exposed to circulating antimicrobial therapy; treatment may require higher blood
levels in order to achieve a therapeutic effect in these locations. Finally, most of the anti-fungal agents work best when they work in concert with the patient's own immune system; simple administration of the anti-fungal is usually not enough.

Similarly, the mechanism of resistance to anti-fungals differs from bacterial resistance to antibiotics. Fungi lack the phage transfer mechanism of horizontally spreading the genetic material coding for resistance. Fungi cannot spread a resistance mechanism from one strain to another, and the efficient mechanism for rapid spread between patients is lacking. Resistance develops through a process of “micro-evolution” and spread from one patient to another is usually the result of cross contamination. Although this process is slow and deliberate relative to spread of bacterial resistance mechanisms, it also means that it is more specific to the particular environment in which it develops, and its eradication requires prolonged, intensive effort.

In addition to the induction of resistance caused by the need for anti-fungal therapy, the global widespread use of anti-fungals in agricultural applications has a particularly important role in emerging patterns of resistance (Verweij et al. 2009). While pan-resistant strains continue to pose their greatest threat to immunocompromised individuals, a significant number of people no such history are infected annually at growing rates and with high levels of morbidity and mortality.

b. Public health threat

The elderly, people undergoing surgery, previous transplant recipients, cancer patients, HIV/AIDS patients, and infants hospitalized in neonatal intensive care units represent increasing proportions of our population who have compromised immune systems and who face the greatest initial risk from these virulent pathogens. Antibiotics represent an important part of the infrastructure necessary for many of these medical interventions we have come to take for granted. Patients benefiting from these interventions are far from being the only people at risk, however. All of the ESKAPE bacteria have been found to have some degree of endemic existence in the community, and all have been found responsible for localized outbreaks in populations with normal immune systems. Community acquired MRSA (CA-MRSA) is now known to affect persons with no evidence of concomitant disease or risk factors and may lead to severe illness and death (Frazee et al. 2005, Maree et al. 2007).

The rise of globalization and subsequent increase in migration, trade, and travel means that no country can isolate itself from resistant bacteria. The person-to-person mode of transmission of many infectious diseases makes the appropriate management of any individual patient a truly public health issue.

c. National security threat

Drug resistance is not only a public health problem, it is also a potential national security threat. Virtually all of the antibiotic-resistant pathogens that occur naturally today can be bioengineered through forced mutation or cloning, and existing weapons-grade pathogens could be manipulated to become resistant to all currently available antibiotics. In the wake of SARS and the 2009 H1N1 avian flu scare, in October 2011 Congress authorized the Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, which provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.

BARDA manages Project BioShield, which includes the procurement and advanced development of medical countermeasures for chemical, biological, radiological, and nuclear agents, as well as the advanced development and procurement of medical countermeasures for pandemic influenza and other emerging infectious diseases that fall outside the auspices of Project BioShield.

d. Cost to U.S. healthcare system; economic burden

The CDC estimates that healthcare-acquired infections cost hospitals in the United States between $35.7 and $45 billion annually. Antibiotic-resistant organisms make up a large part of these infections and result in an estimated 8 million extra days of hospitalization. The portion of excess cost attributable to resistant organisms exceeds $20 billion annually (Hughes 2011). These costs do not account for antibiotic-resistant infections, which originate outside of the hospital setting.

Arguably, the human costs are even greater. Antibiotic-resistant organisms account for an estimated 2 million hospital-acquired infections annually and result in more than 100,000 deaths. The treatment of these infections delays recovery and may impair
complete recovery of patients hospitalized for other unrelated conditions. Efforts to treat highly-resistant organisms with broad spectrum antibiotics accelerates the emergence of even more resistant and virulent organisms which expose even greater populations to risk of exposure and the resulting consequences (Klevens et al. 2007).

c. Challenge in wounded soldiers and other victims of trauma

Antibiotics have revolutionized the treatment of battlefield injuries and other sources of trauma. Infection used to be the major source of morbidity and mortality in victims of injury during war. The early administration and near universal use of antibiotics in wounded soldiers has contributed to a major reduction in impairment and death rates in military personnel. In fact, one of the earliest demonstrations of the benefits of penicillin was at the Anzio landings in Italy in 1943, where its use as a powder dusted on gunshot and shrapnel wounds dramatically eliminated fatal wound infections due to gas gangrene.

Military medicine has not been spared the changing landscape of microbial resistance, however. Bacterial organisms, which were never seen in wounded soldiers, are now seen with regularity. When these previously unusual organisms are isolated, they are often highly resistant to multiple classes of antibiotics. Pan-resistant MRSA and Acinetobacter baumanii are seen regularly in military medical facilities at home and abroad. The latter organism has become so prevalent in one recent conflict that reference to it as “Iraqibacter” has become commonplace. Increasing numbers of extended spectrum beta-lactamase Enterobacteriacea (ESBL), and vancomycin-resistant Enterococcus (VRE) are also being seen in these settings:

![Graph showing emergence and increasing incidence of various resistant pathogens in Iraq and Afghanistan War victims at Walter Reed Army Medical Center from 2000-2006]

Source: Zapor et al. 2008
The advances in trauma care that have led to limb sparing and improved survival are now offset by the complications encountered in treating the new microbe strains (Hansen 2008). The virulence of these organisms in individuals who were previously healthy and not in traditional risk groups of people with compromised immune systems is particularly concerning. The capricious and unpredictable nature of trauma incidence means that the entire population is at significant risk.

**f. Dwindling pipeline; few new antibiotic options on the horizon**

As a class of drugs, antibiotics are unique in the certainty of their eventual obsolescence. All microbes are capable of adapting to the environments in which they live, and their rapid rate of growth make these evolutionary changes a speedy process relative to most other organisms. Microbial exposure to antibiotics initiates a selection bias for survival and reproduction of organisms resistant to the drug, and assures the development of a bacterial strain which is immune to the lethal effects of the antibiotic used. This process, intrinsic to treatment of infectious diseases, is not seen with most other classes of pharmacologic agents. The sustainability of antibiotics in the treatment of infectious diseases requires that replenishment of new drugs and new drug classes occur as existing therapies lose effect. The current range of FDA-approved antibiotics and slow pace of clinical testing and regulatory approval will not provide a solution to a looming threat. In short, doing nothing is not an option.

Despite the continued need for new antimicrobial agents this field has been all but abandoned by the major pharmaceutical companies. The increased size and cost of clinical trials, the new regulatory uncertainty regarding approval criteria, and the low economic return in the marketplace have combined to drive companies out of antibacterial R&D. The ever-growing gap between the urgent public health need for new antibiotics and the dwindling potential for the development of new antibacterial drugs has resulted in a perilous situation. The reluctance of large pharmaceutical companies to invest in antibiotic development is reflected in the dwindling number of antibiotics approved for use by the FDA over the past 30 years:
Between 1980 and 2003, the FDA approved 57 new antibiotics for use in the United States. The 15 largest pharmaceutical companies were responsible for the R&D of these novel antibacterial agents. The R&D time for taking a new molecule from identification to clinical use is typically about eight years. Given the time required to bring a compound “from the bench to the bedside,” FDA-approved drugs generally reflect pharmaceutical R&D activities over the decade preceding approval. Spellberg and colleagues attempted to project the potential development of novel antibiotics by surveying the R&D activities of leading pharmaceutical manufacturers in 2004. At that time, a total of 315 new molecular entities (NMEs) were reported in the publically disclosed descriptions of the leading 15 pharmaceutical manufacturers. Thirty-one (10%) of these NMEs were categorized as anti-infectives, of which five (1.6%) were new antibacterial agents. None of these agents exhibited novel mechanisms of action or represented a new class of antibiotic. In contrast, there were 17 antiviral NMEs (5.4%), 12 of which were HIV-specific agents (four of which were approved by the FDA in 2003). Six of the 12 anti-HIV agents possess novel mechanisms of action. 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. Finally, in contrast with antibacterial agents, numerous NMEs are listed in development for various diseases that are not as immediately life-threatening as serious bacterial infections.

To confirm that the decrease in antibacterial drug development did not reflect an overall decrease in R&D activity, Spellberg and colleagues documented these expenditures for the 10 largest pharmaceutical companies for which public data were available in both 1998 and 2002. They found that these companies spent $21.9 billion on R&D in 1998, whereas, in 2002, R&D expenditures totaled $28.6 billion (figures adjusted for proper economic comparison). Therefore, overall R&D expenditures increased 31 percent during the five-year period, even while antibacterial drug development was curtailed. The reasons for this shift need to be examined critically and adjustments made in a free-market economy to reverse this life-threatening “antibiotic deficit.” In truth, we need both new life-saving antiviral therapies and new antibiotics. In a well-ordered system there is no reason why the private sector, with the right mix of regulatory, marketplace, and economic incentives, cannot provide both.

Finally, in order to determine whether biotechnology companies were filling the gap created by Big Pharma’s departure from the antibiotic space, Spellberg and colleagues examined the R&D programs of the world’s seven largest biotechnology companies. Of a total of 81 NMEs publicly disclosed to be in development by these companies, only one (1.1%) was a new antibacterial agent (Spellberg et al. 2004).

### Anti-infective new molecular entities

<table>
<thead>
<tr>
<th>Type of agent</th>
<th>No. of NMEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HIV</td>
<td>12</td>
</tr>
<tr>
<td>Other antiviral</td>
<td>5</td>
</tr>
<tr>
<td>Antibacterials</td>
<td>5</td>
</tr>
<tr>
<td>Antiparasitics</td>
<td>5</td>
</tr>
<tr>
<td>Antifungals</td>
<td>3</td>
</tr>
<tr>
<td>Topical</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Spellberg et al. 2004
The vibrant anti-HIV R&D infrastructure represents a sharp contrast to antibacterial drug development. While the public health dangers are comparable, the economic barriers to development are less problematic in anti-HIV R&D. For example, patients infected with HIV take medications daily for life. Therefore, HIV infection, unlike bacterial infections, fits well with the current industry trend emphasizing chronic diseases. On the regulatory front, in order to fast-track anti-HIV drugs, the FDA provided clear regulatory guidance and feasible clinical study requirements. Industry responded with a robust portfolio of new drugs and new drug classes to meet the clinical need. The continued success of anti-HIV drug development indicates that anti-infective research could become attractive to pharmaceutical companies when barriers to drug development are diminished.

III. Need for Incentives

a. Regulatory

While antibiotic drug discovery is challenging, regulatory hurdles raise overall development costs to the breaking point, particularly in a time of tight budgets and shrinking profit margins. The pharmaceutical industry views the current state of FDA regulation of antibiotics as uncertain and unduly risky. The lack of available guidance documents from the FDA regarding which studies (e.g., placebo-controlled vs. noninferiority clinical trials) and evidence the agency considers to be acceptable to demonstrate the safety and efficacy of new anti-infective drugs are cited repeatedly as the most important barriers to new antibiotic discovery (Spellberg et al. 2008, Gilbert et al. 2010). Even when the agency provides guidance, problems arise from perceived inconsistencies in protocol requirements for different companies developing drugs for the same disease states, as well as uncertainty that the trial currently required by the FDA will be accepted in the future when a New Drug Application is ultimately filed.

Meanwhile, on the front lines of medicine, hospitals and laboratories across the country routinely test the effectiveness of a panel of antibiotics against bacterial isolates from millions of patients. This is truly personalized medicine in that, the best drug for the patient is selected from a panel of drugs based upon what effect they have on growth of the infectious organism outside of the patient’s body. At the same time, revolutionary new molecular diagnostic technologies are becoming available that will allow for rapid and immediate identification of the infectious organism, and its sensitivity pattern to various antibiotics, when the patient first presents to a healthcare provider.

Although the field of antibiotic development benefits from this unique ability to model the full effect of an antibiotic in an ex vivo system not possible for other diseases, the regulatory system for antibiotics effectively ignores this preclinical advantage. Although the FDA requires in vitro potency and animal efficacy data, two large and well-controlled phase 3 trials are generally required for each indication; preclinical data provides little or no support for approval. Often, these trials require rigid enrollment criteria, which are not reflective of “real-world” conditions. For example, a clinical trial typically limits the entry of subjects infected with a particular organism in a particular organ system, and who have not received any prior antibiotic therapy. Patients developing a multi-resistant bacterial infection vary in organ system involvement, and nearly all have been treated previously with an antibiotic. Effectively, then, the FDA’s clinical trial standards exclude most of the patient populations that would be the most suitable candidates for new antibiotics.

Under the best of circumstances, the development of a single new antibiotic takes more than eight years and costs between $400 million and $800 million. The trouble is that from the time a candidate molecule is identified for use as an antibiotic, until the time it receives FDA approval, the bacteria have time to change and develop resistance to the new compound. Recognizing the urgency of the antibiotic resistance dilemma and the capacity of the targeted disease to change rapidly over time, the FDA should revise and streamline the antibiotic development and approval process.

The FDA has a dual mandate to protect patients and to promote the public health. In its zeal to assure the safety of newly developed antibiotics, it is failing to deliver life-saving therapies and it is allowing the public to be exposed to an ever-increasing threat. The great public health need for new antibiotics and a sustainable pipeline requires coordinated, innovative solutions. Regulatory reform has the potential to play a key role. A review and update of existing regulatory guidance is needed so that the development community can then structure clinical programs in the most effective manner possible. As part of the FDA’s risk-
Benefit calculations, regulators need to consider the important clinical, public health, and national security benefits antibiotics provide when they develop guidance for the design of clinical trials. Failure to encourage innovation of new and safe antibiotics will result in a worsening situation and potential public health disaster of epidemic proportions. These badly needed new antibiotics also need to be used sparingly and only when they are likely to be the most effective option.

The current state of guidance for industry creates an unpredictable regulatory environment that increases risk and discourages the sustained research effort needed to develop novel antibiotics. It is essential that regulatory guidance permits the study of new antibiotics in a real-world practice scenario for the patient population. For example, permitting the enrollment of patients who failed prior antibiotics treatment addresses a critical issue typically not studied in controlled clinical trials.

Specific reforms that would improve both the development of critical antibacterials and the totality of the regulatory review include:

1. **Consideration of preclinical and clinical data for approval**
   Preclinical potency, animal efficacy, and secondary clinical outcomes such as bacterial eradication should all be considered in a systematic review. The requirement for a single well-designed phase 3 trial should be sufficient.

2. **Feasible phase 3 trial designs**
   Trials for approval should be designed which utilize appropriate patient cohorts consistent with the frequency and severity of the disease. The FDA should eliminate the requirement that patients infected with resistant organisms be excluded from the analysis of the control group but not the experimental group. This statistical bias is illogical and loads the dice against an objective assessment of the experimental antibiotic.

3. **Pool data for different indications for uncommon conditions**
   The agency should permit development of a trial design for uncommon resistant pathogens that allows for pooling of data on drug-resistant isolates treated in different indications. This approach would allow for a multiple drug-resistant indication independent of body site in selective situations for rare, resistant pathogens.

4. **Expedited approval for targeted indications**
   The discretionary use of expedited review, accelerated approval and fast-track designation, which are within the discretionary power of the FDA and can make a huge difference in accelerating antibiotic approval times. The FDA has seldom used these tools in the area of antibiotics but it has used them liberally and successfully in other areas of high unmet medical need. These changes that could have dramatic benefit, do not require new legislation, only increased oversight and accountability within the FDA’s present structure.

5. **Expanded use of post-marketing studies**
   Decreasing regulatory hurdles required to achieve FDA approval does not eliminate the necessity of continued assessment of drug safety. Post-marketing trials shift the data collection from the pre-approval process resulting in earlier commercialization. These trials would allow for a much larger database to be accumulated, while enrolling patients in more realistic trial conditions. The concept of conditional approval can also be examined in which following “conditional approval,” the true safety and efficacy pattern of the new antibiotic can be more accurately assessed in a larger, more representative population of patients with infectious disease.

These areas are within the authority of FDA to implement using available regulatory tools. New regulatory pathways could incorporate key ideas from existing mechanisms for accelerated development, orphan drug designation and approval of emerging pathogens indication for antibiotics of critical need. In all cases, it is essential that FDA, physicians and public health officials, along with industry, act as partners with the common goal of enhancing the nation’s health by responding to the ever-growing need for new antibiotics.

b. **Intellectual property protection/Market incentives**
   Patents and data exclusivity work in a similar fashion but are distinctly different from one another. Patents may be granted by the Patent and Trademark Office any time along the development timeline of a drug and can encompass a wide variety of claims. Patents for drugs typically expire 20 years after the date of filing. A drug developer’s patent protection, therefore, depends on the time required for development. Data exclusivity,
in contrast, refers to the exclusive rights to a manufacturer’s clinical data granted by the FDA upon approval of a drug and can run concurrently with a patent or not. Since clinical trials are so expensive and time consuming, the value of the clinical data they generate is very great. Manufacturers naturally regard the data as proprietary, and seek to protect it. This term can be modified by a number of factors. A new chemical entity granted approval at the FDA is given exclusivity for a total of five years under the current Hatch-Waxman provision. This has been modified successfully for some classes of drugs in order to provide incentives for drug companies to develop treatments for targeted diseases for which drug development would be otherwise unprofitable. Examples include the Orphan Drug Designation program, and the Pediatric Drug Exclusivity Provisions.

Because the current market and regulatory system have failed to generate the antibiotics we need, it is reasonable to propose new incentives for manufacturers. The Generating Antibiotic Incentives Now (GAIN) Act (see below) represents an attempt to promote antibiotic development by extending the data exclusivity period, promising a longer term of market protection for approved products where there is a critical unmet need. An alternative to data exclusivity extensions would be extensions of patents themselves, although there are few precedents upon which such a model might be constructed.

c. Economic incentives

In addition to extending the duration of proceeds from antibiotics developed successfully through market exclusivity measures, economic incentives — directed at assuring a robust reentry and commitment of pharmaceutical companies — is also warranted. The IDSA has identified a number of potential inducements to this campaign (Spellberg et al. 2008):

i. Tax credits
Establish R&D tax credit for priority antibiotics and other tools.

ii. Development grants
Fund grants to encourage clinical development of priority antibiotics and other tools.

iii. Market guarantees
Establish federally funded advanced purchase commitments or other promised markets for priority antibiotics and other tools.

iv. National security inclusion
Expansion of the definition of countermeasures found in BARDA to include priority antibiotics that treat “resistant bacterial pathogens that threaten the lives of a significant number of U.S. citizens annually.” This would recognize the clear national security threat that the problem of antibiotic resistance poses to our population.

v. Transferable priority review vouchers
Such vouchers would be provided to pharmaceutical companies that receive FDA approval for a priority antibiotic or related diagnostic product. The company could use the voucher to expedite FDA review of another product of its choice.

vi. Transferable patent extensions
These instruments, also known as “wild card patent extensions,” would grant companies receiving FDA approval for a priority antibiotic an extension on patent time of six months to two years on another drug that the company markets. IDSA currently is not aggressively pursuing adoption of the transferable patent extension concept because of the controversy that has been associated with this idea. However, of all of the potential solutions, transferable patent extensions are generally acknowledged by pharmaceutical companies to be, by far, the incentives most likely to stimulate new antibiotic development. Although many fear the costs to society incurred by extending patents on blockbuster drugs, it is possible that a compromise could be reached by capping the earnings resulting from patent extension. Opponents of transferable patent extensions have characterized the idea as a handout to the pharmaceutical industry. What has been generally underappreciated in this controversy is the potential for newly developed antibiotics to mitigate the dramatic costs posed to society by antimicrobial resistance. Indeed, an academic analysis of the transferable patent extension concept has indicated that it likely would result in a net savings of billions of dollars in healthcare costs by promoting the availability of antibiotics to fight costly multi-drug resistant infections (Spellberg et al. 2007).

At a time when skepticism about government involvement in the marketplace is high, it is reasonable to ask whether market forces alone can address the growing shortage of effective antibiotics. Based on the experience of the past 20 years, it seems evident that the combination of excessive regulatory risk at the FDA and the absence of an attractive business model that offers investors adequate risk-adjusted returns have resulted in a weak market
that is not producing the antibiotics society needs. The public health need is obvious and increasing. So, as with government funding of public goods such as basic research (through the National Institutes of Health) and national defense, there is a compelling case for government to step into the breach. The question is not whether government should intervene, but rather which interventions are most likely to spur essential drug development without disrupting other aspects of the market.

At first glance, some or all of these economic incentives might seem to favor large pharmaceutical companies, perhaps even to the disadvantage of the smaller biotechnology companies where most early risk and discovery now occurs and where transferrable instruments would seem to hold little value. In fact, the opposite is true — the encouragement of pharma’s re-entry into the antibiotic arena would stimulate discovery at every level. Indeed, Big Pharma and small biotech have created a symbiotic relationship. Biotech firms excel at identifying promising new inventions, many of them in university laboratories, and doing the startup work required to translate academic science into commercial products. Since drug development is such a long and costly process, however, it is common for biotech companies to collaborate with large pharmaceutical manufacturers who have the cash and later-stage development expertise necessary to move a product through the pipeline.

The stakeholders who stand to lose the most are the generic drug manufacturers, where virtually no discovery and innovation takes place. Any patent or data exclusivity extension provisions delay entry of generic products into the marketplace, and serve to support higher prices for branded drugs. But in this instance, generic manufacturers stand to lose in any event, as the antibiotics in their portfolios become inactive against resistant pathogens and new drugs are not developed to replace them. In addition, it is often imperative in some cases that we restrict the widespread use of old generic antibiotics, or their use in animal feed supplements, in order to reduce the emergence of antibiotic resistance.

IV. Antibiotic Resistance and Animal Feed

There is growing concern about bacteria found in our food supply that cannot be treated with antibiotics. A study in 2011 by a nonprofit research center in Phoenix analyzed 80 brands of beef, pork, chicken and turkey from five cities and found that 47 percent contained Staphylococcus aureus. These bacteria cause a number of disorders in humans, from skin infections to pneumonia. But their most serious association is with sepsis and systemic inflammatory response syndrome, often called blood poisoning. Of those bacteria, 52 percent were resistant to at least three classes of antibiotics. As Mark Bittman wrote recently in the New York Times, “Consumers who purchase certain ground meat products at the supermarket have a 25 percent chance of ingesting a potentially fatal bacterium that cannot be treated with available antibiotics.” (Mark Bitman, “Bacteria 1, FDA 0,” New York Times December 27, 2011)

The problem is that some 80 percent of the antibiotics sold in the U.S. are given to farm animals. These drugs are administered in low doses prophylactically, which fatten the animals quicker and mitigate infections that naturally arise from unsanitary conditions found in many large-scale farms. Unfortunately, these farms become perfect breeding grounds for bacteria to gain resistance to the drugs.

In 1977, the FDA, aware of the health risks of administering antibiotics to healthy farm animals, proposed to withdraw its prior approval of putting penicillin and tetracycline in animal feed. At the time, the agency published two “notices of opportunity for a hearing” to explore the issue. But the hearings were put on hold by Congress until further research could be conducted. Under pressure from the food industry, the matter was tabled until December 2011, when the FDA at last decided to withdraw its notices. Over 34 years, the problem of bacterial drug resistance in the feed animal population got worse, not better. The FDA tacitly acknowledged this in 2010 when it issued a draft guidance proposing that farmers voluntarily discontinue the use of low-dose antibiotics in healthy animals. “The development of resistance to this important class of drugs,” the FDA wrote, “and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat.” Notably, in 2006, the European Union banned the practice of plying farm animals with antibiotics. Here, however, the FDA, struggling not only to regulate food, drugs, cosmetics, and medical devices, but also tobacco, lacks the political clout to win a battle with agribusiness.
V. Generating Antibiotic Incentives Now (GAIN) Act

To address a growing public health catastrophe, bipartisan champions in the U.S. House of Representatives, led by Dr. Phil Gingrey (R-GA) and Sens. Richard Blumenthal and Bob Corker, recently introduced the Generating Antibiotic Incentives Now (GAIN) Act that seeks to spur development of new antibiotics. The legislation provides the necessary economic incentives so innovator companies are willing to make the necessary investment — without putting federal dollars at stake. (Corker, Blumenthal; The Hill, February 8, 2012.) In particular, the bill seeks to expedite approval of antibiotics against targeted pathogens (the ESKAPE bacteria and multi-drug resistant tuberculosis). In particular, the bill would: 1) Extend the Hatch-Waxman provisions related to data exclusivity by five years, plus six months of additional exclusivity for products with companion diagnostic tests, 2) Provide priority review by the FDA, 3) Make products eligible for fast-track designation by the FDA, and 4) Require a review of FDA guidelines regarding requirements for approval of antibiotic drugs. At present, the bill has broad bipartisan support as it accomplishes many of the goals of encouraging antibiotic development without adding any additional funding commitments.

The GAIN Act represents an important step in the right direction. This pending legislation enjoys strong bipartisan support in both the House and the Senate. Both Democrats and Republicans have coalesced around this legislation. The legislators have been joined by an large and diverse group of supporters, endorsed by 49 organizations across the country including the American Medical Association, The Pew Charitable Trusts, the American Society for Microbiology, St. Jude Children’s Research Hospital, the TB Alliance, Kids v. Cancer, as well as numerous veteran organizations and several small biopharmaceutical companies. More may need to be done, however, to further improve FDA processes and management to better reflect the rising and urgent medical and public health needs resulting from regulatory uncertainty and unpredictability in the antibiotic space. In addition, the recognition that a resurgence of research and discovery within the broad domain of microbial resistance will lead to unanticipated benefits, the creation of incentives at a wider group of targeted pathogens (including fungal pathogens) is warranted.

VI. IDSA’s “10 x ‘20” initiative

In 2010, the IDSA announced its “10 x ‘20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020 (Gilbert et al. 2010).” In achieving consensus among a large variety of key stakeholders in the infectious disease field, it promoted the re-establishment of a sustainable global antibacterial drug R&D enterprise with the power in the short-term to develop 10 new, safe, and effective antibiotics by 2020.

While falling short of making specific recommendations, it identified important entities which need to participate in the policy making decisions that will affect the outcome:

- The executive branch of the government (both U.S. and global counterparts), including the U.S. Department of Health and Human Service’s Food and Drug Administration, Biomedical Advanced Research and Development Authority, National Institutes of Health, Centers for Disease Control and Prevention, and Department of Commerce
- Congress and global counterparts
- The pharmaceutical and diagnostics industries
- Healthcare providers (including those engaged in cancer care and treatment, surgery, pediatrics, transplantation, and infectious diseases) and their professional societies
- Policy and legal communities (including experts in pharmacoeconomics, intellectual property, and reimbursement policy)
- Medical universities and independent research institutes
- Medical and public health philanthropic organizations
- Affected patient advocacy groups

The goal of the IDSA is a noble one. As always, though, the devil will be in the details. The announcement of the initiative is lacking in specific recommendations, and undoubtedly competing interests and objections will arise as the program moves forward. Recognition of the problem’s magnitude as well as the moral and ethical necessity of its solution should help mitigate these factors. Congress has within its remit, and at little or no additional cost to the American taxpayer, the ability to promote these recommendations by enacting the GAIN Act.
VII. Responsible Stewardship

The growing threat of microbial resistance is in large part due to the overuse and misuse of antibiotics in both people and animals. By weight, 80 percent of the world’s antibiotics are administered to livestock and poultry. More tetracycline is given to animals than all antibiotics combined are given to humans. The vast percent of antibiotics administered to animals are not given to treat disease; rather, they are given most often to hasten the rate at which the animals grow. An effective stewardship program will require a dramatic reduction in antibiotic use to promote growth in animals. The Preservation of Antibiotics for Medical Treatment Act is an example of governmental efforts in this regard.

If the use of antibiotics in animal feed is one source of resistance, the overuse of antibiotics in treating common illnesses is another. Only about 5 percent of bronchitis cases are caused by a bacterial infection, and antibiotics have no effect upon viral infections such as the common cold. Most cases of bronchitis are caused by a viral infection and are self-limited; they resolve of their own accord in a few weeks. The use of antibiotics to treat bronchitis is to be considered unnecessary. Antibiotic treatment does not help the overwhelming majority of sore throats. Acute sinusitis is caused by bacteria less than 5 percent of the time, and antibiotics are proven ineffective for most cases. Despite these facts, patients who seek medical attention for any of these conditions are prescribed an antibiotic almost 80 percent of the time. When an antibiotic is prescribed, a broad-spectrum antibiotic is selected most often. This is thought to be the driving force behind the emergence of fluoroquinolone resistance.

Physician and patient education about antibiotic use and misuse may have some impact on diminishing human exposure to antibiotics unnecessarily. The CDC’s “Get Smart—Know When Antibiotics Work” campaign is one such example. Continued patient expectations and physician prescribing habits would suggest that such efforts will be incomplete, however. Evidence-based control of antibiotic prescribing may be possible as electronic medical records and prescribing are adopted. Increased vigilance by pharmacies, especially by hospital pharmacies, have an important role to play in monitoring and calling attention to unnecessary or excessive antibiotic prescribing patterns by physicians. Hospital and pharmacy benefit manager (PBM) formularies, overseen by multidisciplinary teams, have been proven effective in reducing indiscriminate and inappropriate antibiotic usage. Finally, the release of newly approved antibiotics in parenteral, but not oral formulations, may limit the use of these new agents in advanced care settings. Appropriate pricing structure will be necessary in order to assure profitability in the development of these limited access antibiotics. The market and pricing incentives must be created to allow for premium pricing and hopeful restricted use of the new generation of intravenous antibiotics targeted against the ESKAPE bacteria and MDR TB.

Overuse does not cause resistance; it merely hastens its development. Therefore, stewardship may mitigate the problem, but it will not eliminate it. It does not negate the need for continued development of new compounds. The restrictions on the use of new antibiotics are an essential part of the approach of “antibiotic stewardship” used to prevent development and spread of resistance. While stewardship may delay the development and spread of resistant bacteria, it may also have as an unintended consequence a further reduction in the economic value of new antibiotics. Thus, an even more pressing need for predictable and feasible paths for the development of new drugs is identified.

VIII. California Landscape

California is home to the largest concentration of biomedical R&D in the U.S. California’s biomedical companies have estimated revenues of $115.4 billion, 1,365 products in the product pipeline, and have become an increasingly important component of the region’s economy. With a proven ability to risk and innovate, the California biomedical community will likely play a key leadership role in any anti-infective initiatives moving forward. The co-location of world-class academic centers, entrepreneurial scientists, and a large concentration of venture capital make the region a fertile center of innovation and advances in solutions to healthcare problems.
IX. Summary

The effective treatment of infectious disease employs the use of antibiotics. There is a declining supply of these agents, however, and an increasing incidence of bacteria resistant to their effects. The rapid emergence on a global basis of bacteria resistant to all known antibiotics has created a looming public health crisis that is affecting all hospitals and communities in the U.S. Regulatory and market forces have led to an exodus of major pharmaceutical companies from the field. As a result, there are very few novel antibacterial agents in clinical development. If the development of antibiotics was an important legacy of the last epidemiologic transition, the rise of antibiotic resistance is a harbinger of the next one. We know that infectious diseases will always be with us, and that they will evolve in ways that are often beyond our direct control.

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