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U.S. Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Stimulating Innovation in Medical Technologies [Docket No. 2004S-0233]

To Whom it May Concern:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on the Department of Health and Human Services (HHS) initiative to stimulate innovation in medical technologies. Specifically, we would like to present the Society's views on the critical need for new drugs, vaccines and diagnostics to treat, prevent, and detect infectious diseases agents, and particularly for antibiotics to treat resistant bacterial infections as well as new rapid diagnostics to detect them.

IDSA represents nearly 8,000 physicians and scientists devoted to patient care, education, research, and community health planning in infectious diseases. The Society's members focus on the epidemiology, diagnosis, treatment, prevention, and investigation of infectious diseases in the U.S. and abroad. Our members include researchers who study infectious microbes, including agents of bioterrorism as well as naturally occurring microbes. Our members also include scientists involved in the development of new pharmaceuticals and vaccines. Also among our members are the ID clinicians who will be integrally involved should a bioterrorism event or spontaneous natural outbreak occur—an ID specialist discovered the anthrax case that occurred in Florida in 2001. ID clinicians care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, those with cancer or transplants who have life-threatening infections caused by unusual microorganisms, food poisoning, and HIV/AIDS as well as new and emerging infections, such as severe acute respiratory syndrome ("SARS") and West Nile virus. Housed within IDSA is the HIV Medicine Association ("HIVMA"), which represents physicians working on the frontline of the HIV/AIDS pandemic. HIVMA members conduct research, administer prevention programs, and provide clinical services to individuals with HIV/AIDS. Together, IDSA and HIVMA are the principal organizations representing infectious diseases and HIV physicians in the United States.

In addition to our membership, IDSA's comments below support the needs of patients in the United States and throughout the world who have suffered from painful and life-threatening infections caused by microbial pathogens. These patients often suffer in silence. It is our intention to make policymakers aware of these patients' plights, most of which could be mitigated through the availability of effective treatments, and to ask that you respond quickly with thoughtful and effective solutions.

Comments

We applaud Secretary Tommy Thompson for establishing a high-level task force with the charge of seeking new opportunities to promote speedier access to new innovative medical technologies. We deem this effort to be critically important as new medicines and diagnostics are desperately needed to use against naturally occurring infections. The recent shortage of influenza vaccine is just one example of the problems that exist in infectious diseases-related product pipelines.

The HHS task force can serve a pivotal role in addressing the dearth of new infectious disease products by encouraging President Bush to submit a legislative proposal to Congress that includes solutions to spur research and development (R&D) across the spectrum of infectious diseases medicine. IDSA has outlined in our comments below several legislative solutions for the task force to consider. Current congressional activity related to the development of new legislation, commonly referred to as "Bioshield II," provides an excellent window of opportunity for policymakers to act to address the current stagnation in the R&D pipelines for new antiinfectives and diagnostics. HHS task force members also can work to integrate the administrative solutions outlined in our comments for the Food and Drug Administration (FDA) and National Institutes of Health (NIH) to begin to address the problem.

The Administration and Congress worked together over the past 20 months to enact the "Project Bioshield Act of 2004" ("Bioshield I"), a critically important and creative mechanism that will motivate the pharmaceutical and biotechnology industries to begin to address the threat of bioterrorism. In our opinion, however, "Bioshield I" did not go far enough, as it does not address the threats to U.S. patients posed by naturally occurring infections.

On July 21, 2004, the same day that President Bush signed "Bioshield I" into law, IDSA issued its landmark report entitled, "*Bad Bugs, No Drugs, As Antibiotic Discovery Stagnates, A Public Health Crisis Brews,*" which calls attention to a steep decline in industry R&D of new, effective antiinfectives intended to treat naturally occurring infections. IDSA's report supports the development of new medicines and diagnostics to treat, prevent, and detect all infectious diseases, but specifically highlights the pharmaceutical and biotechnology industries' decreasing commitment to antibiotic R&D. In recent years, companies have either withdrawn or seriously downsized their dedicated resources and staff from antibiotic development. The withdrawal of industry from this critical area of medicine, coupled with evolving microbial resistance to available antibiotics, poses a significant public health problem. Infectious diseases and HIV

physicians on the frontline of patient care see patients every day who face lengthy and expensive hospitalizations, painful courses of treatment and even death because of drug-resistant and other infections. We desperately need new weapons to protect these patients from naturally occurring infections.

Market forces alone will not solve the current crisis in infectious diseases drug, vaccine and diagnostic R&D—that’s why we need innovative public policy changes. There is an inextricably linked, synergistic relationship between naturally occurring infections and bioterrorism agents. Given the public health implications, we believe that similar approaches can be taken to spur the development of therapies in both areas at the same time. Members of Congress are beginning to see the connection between naturally occurring infections and bioterrorism and understand our vulnerability. In their reports on “Bioshield I” in 2003, both the House Government Reform Committee and the Energy and Commerce Committee linked *natural conditions*, including antimicrobial resistance and dangerous viruses, to national security concerns. The Energy and Commerce Report stated “advancing the discovery of new antimicrobial drugs to treat resistant organisms ... may well pay dividends for both national security and public health.”

We urge the HHS task force to consider the problems outlined below and the proposed administrative and legislative solutions described on page 6.

Why Policymakers Should be Concerned About Naturally Occurring Infectious Diseases

While Congress’ and the Administration’s recent actions on “Bioshield I” are highly appropriate, it is important to keep things in perspective. Not one American has died from bioterrorism since President Bush first announced the need for “Bioshield I” in February of 2003, but drug-resistant bacterial and other infections have killed tens, if not hundreds, of thousands of Americans in hospitals and communities across the United States and millions of people across the world during that same short period of time.

Here are some important facts about naturally occurring infectious diseases reported by the World Health Organization and others:

- Infectious diseases are the second leading cause of death in the world and, by far, the leading cause of premature death and disability.
- Worldwide, 15 million deaths annually are caused by infectious diseases.
- Three of the biggest killers—HIV, tuberculosis (TB) and malaria—account for nearly 40 percent of deaths caused by infectious diseases (5.6 million deaths in 2001).
- Diarrheal diseases and respiratory infections are equally as deadly, accounting for 5.8 million deaths in 2001.
- Influenza accounts for 36,000 deaths and more than 200,000 hospitalizations in the United States and 250,000 to 500,000 deaths globally each year. A pandemic influenza outbreak could kill millions in the U.S. alone.
- “Neglected” infectious diseases that primarily affect the poorest populations living in remote areas of the world leave nearly 1 billion people with a lifetime of debilitating illnesses and deformities. These diseases include lymphatic filariasis

- (5.6 million disability life adjusted years [DALYs—the number of healthy years of life lost due to premature death and disability]), intestinal nematode infections (4.7 million DALYs), leishmaniasis (2.4 million DALYs), schistosomiasis (1.8 million DALYs), sleeping sickness (1.6 million DALYs), onchocerciasis (1.0 million DALYs), dengue (0.7 million DALYs), chagas disease (0.6 million DALYs), and leprosy (0.2 million DALYs). Despite this enormous disease burden, very few public or private resources have been devoted to research on these diseases.
- According to the Global Forum for Health Research, only about 10 percent of health research funding is targeted to diseases that account for 90 percent of the global health burden.

Emerging and Re-emerging Infectious Diseases

Robust R&D programs are needed to respond successfully to existing infectious diseases as well as new threats on the horizon. More than three-dozen new infectious diseases have been identified since the 1970s that have impacted the United States and more vulnerable countries. The list includes HIV/AIDS, SARS, West Nile virus, Lyme disease, hepatitis C, a new form of cholera, waterborne disease due to *Cryptosporidium*, foodborne disease caused by *E. coli* 0157:H7, and a plethora of neglected diseases that primarily affect patients in developing countries.

Some of these diseases have no treatment except for supportive care. For diseases that do have effective treatments, complacency can stifle new research and allow us to be caught off guard when current treatments become less effective due to resistance. This has been the case with tuberculosis (TB). It has been 30 years since a new class of antibiotics was approved to treat TB despite the fact that it is the second most common microbial cause of death in the world. Doctors also are concerned about the rapid rate at which other bacterial infections, such as gonorrhea and syphilis, are becoming resistant to drugs. Finally, for diseases such as TB, AIDS, and malaria, which have notoriously complex and sometimes toxic treatment regimens, there is a substantial need for new drugs that are not only more effective but easier to deliver to the patient so that greater drug adherence and, ultimately, successful care and treatment will be achieved.

Antibiotic-Resistant Bacterial Pathogens

Here are some surprising facts about drug-resistant bacterial infections in the United States:

- Infections caused by resistant bacteria can strike anyone—the young and the old, the healthy and the chronically ill. Antibiotic resistance is a particularly serious problem for patients whose immune systems are compromised, such as people with HIV/AIDS and patients in critical care units.
- About 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug. The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating.

- Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. The total cost to U.S. society is nearly \$5 billion annually.
- The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs simply are not as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.
- Resistant bacterial infections are not only a public health problem; they have national and global security implications as well.
- The Institute of Medicine (IOM) and federal officials have identified antibiotic resistance and the dearth of antibiotic R&D as increasing threats to U.S. public health.

Until recently, company R&D efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. Infectious diseases physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future. There simply aren't enough new drugs in the pharmaceutical pipeline to keep pace with drug-resistant bacterial infections, so-called "superbugs."

A recent analysis published in the journal *Clinical Infectious Diseases* found only five new antibiotics in the R&D pipeline out of more than 506 drugs in development. The authors evaluated the websites of 2002 annual reports of 15 major pharmaceutical companies with a track record in antibiotic development and seven major biotechnology companies. Their analysis revealed four new antibiotics being developed by pharmaceutical companies, and only one antibiotic being developed by a biotech company. By comparison, the analysis found that the pharmaceutical companies were developing 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders, and 32 for pulmonary disease. The biotech companies were developing 24 drugs for inflammation/immunomodulators, 14 drugs for metabolic/endocrine disorders, and 13 for cancer.

The end result of the decline in antibiotic discovery research is that FDA is approving few new antibiotics. Since 1998, only 10 new antibiotics have been approved, two of which are truly novel—i.e., defined as having a new target of action, with no cross-resistance with other antibiotics. In 2002, among 89 new medicines emerging on the market, none was an antibiotic.

IOM's 2003 report on microbial threats reinforces the point, noting that although at first glance the situation with respect to antibiotics currently in clinical development looks encouraging, not one *new class* of antibiotics is in late-stage development. "Rather these 'new' antibiotics belong to existing classes, including macrolides and quinolones, that have been used to treat humans for years," IOM said.

Unfortunately, both the public and private sectors appear to have been lulled into a false sense of security based on past successes. The potential crisis at hand is the result of a marked decrease in industry R&D, government inaction, and the increasing prevalence of resistant bacteria.

Pharmaceutical Charity Helps, But Is Not the Solution

Some policymakers and members of the public place the onus on the pharmaceutical industry, saying that companies should act responsibly and ensure that new drugs and vaccines are available as needed. The pharmaceutical industry supports many good works *pro bono*. Some examples include Merck & Co.'s efforts related to River Blindness; efforts by Bristol-Myers Squibb, Pfizer, and other drug companies related to global AIDS; and GlaxoSmithKline's malaria and AstraZeneca's TB drug discovery initiatives. Nevertheless, companies are responsible to their shareholders and cannot alter their fundamental business strategies in ways that would place their bottom lines at risk. Drug and vaccine R&D is expensive, risky, and time-consuming. As such, companies are most likely to invest in products for which a strong return on investment is likely, such as drugs that treat long-term, chronic illnesses, lifestyle issues, and products that benefit people in developed countries who can afford to pay for them. In contrast, most anti-infectives, particularly antibiotics, are used only for short durations (7-14 days). Further, many of these drugs face restricted use in order to avoid the development of resistance. Eventually resistance also limits the effectiveness and profitability of an antibiotic. Finally, reliance upon market forces alone has resulted in vaccines and medicines desperately needed in the developing world being left out.

Policymakers and the public should have no illusions that future pharmaceutical charity will be sufficient to address the existing and emerging infectious pathogens that threaten U.S. and global health. Instead, IDSA believes the onus is on the federal government to reinvigorate industry interest in anti-infective R&D as a means to protect U.S. public health and strengthen national security.

Potential Solutions

IDSA's "*Bad Bugs, No Drugs*" report offers a number of solutions for policymakers to consider. IDSA does not claim to possess all of the answers, but we believe a combination of the administrative and legislative solutions listed below and taken from our report will help. We hope the HHS task force members will take these recommendations and use them to shape a framework for governmental action.

IDSA has investigated the decline in new antibiotic R&D for nearly two years, interviewing stakeholders from all sectors. We have met with officials from FDA, the National Institute of Allergy and Infectious Diseases (NIAID), the Centers for Disease Control and Prevention, congressional members and staff, executives from leading pharmaceutical and biotechnology companies, representatives from public-private partnerships that are focused on infectious diseases-related product development, patients, and other stakeholders. Based on our investigation, IDSA is convinced that the pharmaceutical and biotechnology industries are clearly best situated to take the lead in developing new antibiotics needed to treat bacterial diseases. They are the only player with a track record of success. Consequently, industry action must become the central focus of an innovative federal public health effort designed to stimulate antibiotic R&D.

IDSA's investigation of the problem has revealed that the solutions most likely to spur R&D within major pharmaceutical companies include those that provide financial benefits prior to a drug's approval (e.g., tax credits for R&D), commence at the time of approval (e.g., wild-card patent extension), reduce the costs of clinical trials (e.g., FDA flexibility concerning the evidence necessary to demonstrate safety and efficacy; NIAID-sponsored research to develop rapid diagnostics tests, screen candidates, etc.), and reduce companies' risks (e.g., liability protections). A guaranteed market solution, such as provided in "Bioshield I", also could be helpful to spur the development of influenza vaccine, antibiotics, and other similarly situated products. R&D at smaller biotechnology companies also could be stimulated through statutory and administrative changes. Specific recommendations for FDA and NIAID action are outlined below. Critical priority incentives that we believe will have the greatest impact are indicated.

Administrative Solutions

Food and Drug Administration Recommendations

FDA is a pivotal and constructive partner in the process of antibiotic development. In order to effectively implement FDA's plan, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, modifications to existing policy, procedures, and guidelines are necessary. Each of the following recommendations is a CRITICAL PRIORITY:

- Accelerate the publication of updated guidelines for antibiotic clinical trials to provide needed clarity, and revisit existing guidelines as appropriate to ensure their relevance
- Encourage imaginative clinical trial designs that lead to a better understanding of drug efficacy against resistant bacterial pathogens
- Provide a clear definition of acceptable surrogate markers as end points for clinical trials of bacterial infections
- Explore and, when appropriate, encourage the use of animal models of infection, in vitro technologies, and valid microbiologic surrogate markers to reduce the number of efficacy studies required for each additional indication while maintaining safe and effective drug dose regimens
- Explore with NIAID all opportunities to streamline antibiotic drug development
- Grant priority antibiotics accelerated review status

National Institute of Allergy and Infectious Diseases Recommendations

NIAID could play a central role in the R&D process. To do so, NIAID should implement the following recommendations. Each is a CRITICAL PRIORITY:

- Aggressively encourage translational (bench to bedside) research as described in NIH's *Roadmap for Medical Research*
- Remove roadblocks to antibiotic R&D that may exist in NIAID's structure and guidelines, including any unnecessary restrictions affecting companies' intellectual property rights

- Increase the number and size of grants that support discovery of new drugs that treat targeted pathogens
- Develop and expand collaborations with industry and the infectious diseases research community
- Sufficiently fund and rapidly launch NIAID’s newly established Drug Discovery and Mechanisms of Antimicrobial Resistance Study Section
- Engage outside experts in research planning and ensure more transparent decision-making
- Explore with FDA all opportunities to streamline antibiotic drug development
- Encourage research on topics directly related to conduct of clinical trials
- Sponsor research into new rapid diagnostic tests for bacterial infections that, when available, could reduce the cost of clinical trials
- Encourage research on antibiotic use and resistance development
- Fund placebo-controlled trials to evaluate the necessity of antibiotic therapy for selected diseases

Legislative Solutions

The Administration and Congress also must work together to enact statutory incentives that stimulate the discovery and development of new antibiotics to treat drug-resistant and other dangerous infections.

Advisory Board to Identify Pathogens of Greatest Concern [CRITICAL PRIORITY]
 Establish and empower an independent advisory board that reports to the HHS Secretary to identify those microbial pathogens that most significantly threaten public health. The Secretary would then use the advisory board’s recommendations as a basis for targeting legislative R&D incentives such as those listed below.

Supplemental intellectual property protections:

- “Wild-card patent extension.” [CRITICAL PRIORITY]
 A company that develops and receives approval for a priority antiinfective could extend the market exclusivity period of another FDA-approved drug as long as the company commits to invest a portion of the profits derived during the extension period back into antiinfective R&D.
- Restoration of all patent time lost during FDA's review of and clinical trials undertaken related to priority antibiotics and other antiinfectives
- Extended market and data exclusivity similar to what has been successfully implemented for pediatric and orphan drugs

Other potential statutory incentives:

- Tax incentives for R&D of priority antiinfectives [CRITICAL PRIORITY]
- Measured liability protections [CRITICAL PRIORITY]
- Additional statutory flexibility at FDA regarding approval of antibiotics and other antiinfectives, as needed
- Antitrust exemptions for certain company communications

- A guaranteed market similar to that provided in “Bioshield I” for priority antibiotics that target resistant bacterial, other antiinfectives, and influenza vaccine, as appropriate [CRITICAL PRIORITY]

Establish similar statutory incentives to spur R&D for rapid diagnostic tests for targeted pathogens, which will help to reduce the cost of clinical trials

Potential statutory incentives of interest to small biopharmaceutical companies:

- Waive FDA supplemental application user fees for priority antibiotics and other antiinfectives
- Tax credits specifically targeting this segment of the industry
- Small business grants

Support synergistic partnerships that focus on infectious diseases medicines:

A growing number of international public-private partnerships are focusing on the discovery of medicines to treat infectious diseases in the United States and globally. Initiatives like the International AIDS Vaccine Initiative, the Medicines for Malaria Venture, and the Global Alliance for TB Drug Development offer promising opportunities to advance product R&D in areas that have languished in the past. Public-private partnerships have adopted business models that exploit the venture capital approach to investment in new product R&D. Such initiatives receive the bulk of funding from the public and philanthropic sectors. They involve for-profit partners by seeking in-kind contributions from industry. The commitment of U.S. public dollars for these and similar initiatives would take advantage of the entrepreneurial spirit possessed by many researchers and humanitarians.

In addition to funding public-private partnerships, policymakers should seriously consider ways to prompt companies to inventory their shelves for promising drug candidates that could be donated to the partnerships for development. Such candidates exist, and companies recently have shown some interest in donating them. This is not a current priority for companies, however, because the resources required would have to be diverted from other efforts.

Conclusion

The “bad bugs, no drugs” problem is growing more serious, and patients are suffering. Even if all of the incentives outlined in our comments were implemented today, it likely would take 10 or more years for companies to move safe and effective new drugs, vaccines and diagnostics to market. The federal government must take decisive action now to address the burgeoning problem of infectious diseases, particularly the lack of antibiotics to treat resistant organisms.

Government-sponsored research and refinement of existing regulations, policies, and guidance can help to address the overall problem, fill in some of the gaps in drug, vaccine, and diagnostics development, and help to reduce the cost of discovery and development. Industry action, however, must remain policymakers’ central focus. Policymakers must remove financial disincentives and regulatory barriers to antiinfective

R&D as a means to stimulate pharmaceutical and biotechnology companies to invest in the discovery of tools to treat, prevent, and detect infectious diseases.

Specific to antibiotics, the past two decades of antibiotic development clearly have demonstrated that we no longer can rely on existing market forces to keep companies engaged in this area of drug discovery and development. Should additional companies' antibiotic R&D infrastructures be dismantled, it will take years to establish new programs—or this expertise could simply be lost forever. New antibiotics are desperately needed to treat serious as well as common infections. The bacteria that cause these infections are becoming increasingly resistant to the antibiotics that for years have been considered standard of care, and the list of resistant pathogens keeps growing. It is not possible to predict when an epidemic of drug-resistant bacteria will occur—but we do know it will happen.

Drugs, vaccines and diagnostics also are needed across the spectrum of infectious diseases medicine. Treating, preventing and rapidly diagnosing AIDS, TB, malaria, the neglected diseases found primarily in developing countries, pandemic influenza, and the next emerging infection will require renewed vision, creative policymaking and bold action.

The proposed “Bioshield II” legislation currently being developed provides a critical opportunity to spur the development of new tools to protect Americans and the global community against the scourge of naturally occurring and bioterrorism-related infections. We urge the Administration to show bold leadership by supporting this legislation, including through the development of an Administrative legislative proposal, and promoting its quick enactment.

Without innovative public policy and additional financial support, fewer and fewer antibiotics will be available to treat the increasing number of dangerous microbes. The recommendations IDSA is advancing through these comments are intended to ensure a sustainable supply of safe and effective medicines and diagnostics. With the HHS task force's help, U.S. infectious diseases physicians soon will have the tools necessary to treat the very sick patients currently suffering from serious infections across the United States and globally.

Again, we appreciate the opportunity to comment on this important matter. Should you have any questions, please contact Robert J. Guidos, JD, IDSA's Director of Public Policy and Government Relations, at 703-299-0200.

Sincerely,

Walter E. Stamm, MD
President

