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Political Roulette and the Public Health:
The Impact of Political Intrusions on Drug
Development and the Consequence for
America's Biodefense

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Executive Summary

Project Bioshield was intended to stimulate the production of medical countermeasures to would-be agents of bioterrorism. The legislation was visionary and monumental.¹ But by many accounts, it has been off to a slow start.

There are many reasons. But above all else, developing medical countermeasures is a complicated affair challenged not only by unique science and regulatory requirements, but also politics.

On the science, creating new drugs and vaccines targeted against pathogens that can be used as bioweapons includes all the challenges of creating traditional drugs against traditional diseases, with the added caveat that the weaponized pathogens that you are targeting do not exist in nature.

There can be long lead times needed to develop these new medical products, special medical requirements, and uncertainty over a regulatory process that is not as clearly defined as for conventional drug developers.

On the political side, the marketing of these products is also fraught with uncertainty. It relies on government purchases, and government contracting for these products through a process that is unfamiliar to life science companies and for the government, not as simple as contracting for other defense items like weapons systems and airplanes.

Policies aimed at stimulating development of these products have not fully taken note of these challenges, nor have all of the policy makers, who are rightfully eager to improve America's biodefense, but whose political activity may be undermining the very efforts and outcomes that they aim to promote.

The result is that some of the solutions to these challenges have only served to harden them by injecting political considerations into a drug development process that should be guided by purely by science and the public health imperative.

Indeed, as this paper will note, some recent reports of political intrusion into the scientific process for procuring a new smallpox and anthrax vaccine, as well as countermeasures to radiation poisoning, has added to the cost of capital for these endeavors—in some cases, putting products further out of reach, and in all cases, making would-be investors increasingly reluctant to enter the market for developing bioterrorism countermeasures.

This experience, and the unhelpful impact of politics on drug development, is not unique to medical products aimed at biodefense. It is also occurring in other therapeutic areas where new drug development is marked by a high degree of political interest and public need, including HIV/AIDS and antipsychotic drugs.

Yet in each of these cases, there is one abiding lesson: Political intrusion into drug development only serves to increase the costs, and the uncertainty of coming up with drugs uniquely targeted to these ailments.

In the end, politics becomes one more factor they need to accommodate, amidst challenges of anticipating science and judging the marketplace. Yet politics is the one factor that they are least skilled at managing, and therefore the most eager to avoid. The end result is very clear, as this paper will demonstrate: less development work gets done in therapeutic areas that are in political play. Biodefense is high among them. And in the end, fewer new drugs are developed.

Introduction

In the fall of 2001, Americans were abruptly reminded of two ominous realities of modern microbiology. First, one of the most celebrated acts of bioterrorism made use of sophisticated anthrax spores dispersed by a crude delivery device—the United States Postal System², to reinforce what many inside U.S. defense and public health circles had long feared. Bioterrorism posed an imminent threat to Americans as a result of the world's growing mastery of the science to inexpensively and easily create and deliver such weapons.^{3 4 5}

Second, our immediate response to this act of bioterrorism demonstrated that we were woefully unprepared as a nation for this new kind of war.⁶ There was only one approved drug to treat anthrax infection, and it needed to be started on exposed patients early. The only vaccine was plagued by production problems and controversy. Our ability to provide these products was not any better than the products themselves. Faced with potentially surging demand for an antidote to anthrax, the only company that produced the Food and Drug Administration approved treatment for anthrax infection (Bayer's antibiotic Ciprofloxacin⁷) scrambled to convert to antibiotic production a statin facility that was recently idled as a result of the withdrawal of the cholesterol lowering drug Baycol. Members of the press as well as leaders in the medical profession openly discussed whether the government would need to appropriate Bayer's patent on its antibiotic Cipro in order to ensure lower-cost and predictable procurement of the antibiotic.^{8 9 10 11 12} Canada went so far as to award a \$1.5 million contract to Canadian Generic drug maker Apotex, without the agreement of Bayer, to supply the drug to the Canadian government. (The contract with Apotex was ultimately cancelled).¹³ Moreover, the country's sole manufacturer of the outdated anthrax vaccine, the Lansing, Michigan company BioPort, was mired in financial¹⁴ and production problems, including reports that its sole manufacturing facility, which had been subject to health violations, was contaminated¹⁵ and that several anthrax vaccine lots failed to meet the potency requirement specified by the FDA, which is meant to ensure the vaccine is effective.¹⁶

These challenges made manifest that we were not a nation well prepared to meet this new challenge. And why should we be. Until then, bioterrorism was mostly discussed in academic meetings, not on the evening news.

But the anthrax attacks, and the aggression showed by Al Qaeda, began a new era, and mandated a new preparedness.

Yet our immediate response to the anthrax attacks has brought into question our ability to make sure we are significantly more prepared for this threat than we were almost four years ago. Of all of these responses, one is most often cited by drug developers unwilling to invest heavily in developing new countermeasures—the temptation among some officials, particularly in Canada, to contemplate

appropriating Bayer's intellectual property on Cipro in order to ensure a stable supply and good price immediately after the anthrax attacks. Drug developers say that Bayer's predicament with Cipro underscored the political risk of doing development in a therapeutic space where their only business partners are world governments and their market available only at a time of crisis. This uncertainty continues to color investments in bioterrorism defense today, despite specific measures like Project BioShield, which were undertaken to encourage the private development of biological countermeasures. In an industry already fraught with uncertainty—whether it's the scientific uncertainty of finding an active drug or the regulatory uncertainty of clearing the FDA—political considerations add a new wrinkle that most drug developers want no part of.

Drug companies are accustomed to dealing with scientific and regulatory risk. Political risk adds a new layer that most drug developers believe they are best off avoiding. The American Venture Capital Association, a consortium of the private investors who fund early-stage biotech companies, articulated this trepidation recently. In the group's recent report, "Government Market Enigma Causes Industry to Stick with What They Know", the AVCA concluded that Biodefense "is not an open market; it is 'politically charged with shifting priorities'; and the appropriations cycles lack predictability."¹⁷ The report's authors conclude that Biodefense is unappealing because, in their words, it has only one customer (the US government), low profit margins, political vulnerability, and uncertain liability and patent protection.¹⁸

For these reasons, among others, over the last several years Wall Street has continued to lower its expectations for many once-hot biodefense contractors like Acambis, Avant Immunotherapeutics, and Cepheid. The head of global biotechnology investment banking at Goldman Sachs was quoted as explaining it this way: "There is a perception that the government could step in and limit a firm's ability to develop something commercially that was originally part of a biodefense project... Whether that's right or not, I do think investors and CEOs [who got] caught up in the initial wave of enthusiasm over biodefense are back now to focusing most of their attention on their core business opportunities where the market, not the government, sets the prices—and where there are no questions about restrictions on patents."¹⁹

This political intrusion, and the uncertainty it spawns for investors and drug developers doing business in this area, was seen very recently in the political activity surrounding the government's procurement of a new Anthrax Vaccine as this paper will detail later. In particular were complaints made on Capitol Hill, which weighed heavily on the procurement and development process for this vaccine. When political considerations are imposed on scientific decision-making, and they influence medical decisions made by drug developers and those who use medical products, it serves to ward away drug development efforts. Paradoxically, the political attention paid to areas like bioterrorism defense and the procurement of biodefense products, while well intentioned, often only serves

to undermine the extraordinary effort policy makers have undertaken in recent years to improve the framework for developing these medical products and improving the country's bioterrorism defense.

Project BioShield Marks a Call to Action

Principal among these political efforts to jump start biodefense development was the BioShield Act of 2004. The law was enacted, in large measure, as a response to the need for new generations of countermeasures, and to address the shortcomings in the marketplace that made developing them nearly impossible. The \$5.6 billion federal BioShield program sought to create financial incentives and a guaranteed purchase arrangement for product developers who invested in successful countermeasure development. For example, the law provides a guaranteed market for countermeasures and expedited National Institutes of Health peer-review practices for grants, contracts and cooperative agreements. Both of these provisions have been used to develop and purchase a modern anthrax vaccine as well as fund additional research in the priority pathogens such as smallpox. Some recent assessments have concluded that BioShield is meeting the needs of the near-term threats from the mostly likely or feared pathogens, including anthrax, smallpox and botulism.²⁰

For industry the real key is an advance purchase contract under the BioShield Act. The legislation, in essence, invites companies to approach the government with something more than a good idea, strong pre-clinical and animal data and sufficient clinical data to show that a new compound has a high probability of addressing a WMD threat. If the product meets a defined biodefense need, the government can give the product's developer an advance purchase contract, where government commits today to buy a specified number of doses if and when the product developer is able to deliver a "licensable" product but still in advance of FDA licensure. The government does not pay for products under such contracts until the product receives an "Emergency Use Authorization" which is certification that delivered doses can be transferred into licensed inventory on full FDA approval. Through this arrangement, risk is shifted from the government to the manufacturer. The investor marketplace then does additional due diligence on the new product. If the marketplace does not have confidence that the proposed product can be delivered or that the government will complete its purchase, than the sponsor will be unable to raise the needed funds to continue its development program.

BioShield is not the only Federal effort aimed at stimulating biodefense development. In addition to the BioShield program, other federal money is being directed at earlier stage research into the development of new countermeasures. For example, the Bush administration's biodefense budget for fiscal 2005 is about \$7.6 billion, which is 18 times greater than the biodefense budget from four years ago. About \$1.7 billion will be spent this year in NIH funding alone, almost entirely at the National Institute of Allergy and Infectious Diseases.²¹ Most of that

money will be heavily focused on basic research into the pathogens that are acknowledged to be genuine bioterrorism threats.

All of this spending amounts to a considerable effort to develop new biodefense countermeasures. But what do we have to show for these efforts today? And what are they likely to produce for the future?

As this paper demonstrates, the economic incentives that BioShield established have been largely insufficient to offset the difficulty and uncertainty of working on products that have no established market other than those decreed by politically administered programs. Moreover, political interference into some of the recent contracts awarded under Project BioShield has only served to increase the uncertainty and therefore cost of doing business in this area, while the incentives remain static. It is not immediately clear, either, that the provisions being contemplated as part of a new version of the BioShield legislation will be substantially more successful in traversing these disincentives and inspiring new drug development work.

Complicated Science Adds to the High Hurdles

While political interference into the scientific process of developing biodefense products has played a role in dampening interest in this field, this political uncertainty is by no means the only factor weighing on this market. The fact remains that the serendipity of science means that any large-scale drug development effort is fraught with uncertainty. The familiar statistics, that only about one in every one hundred new compounds that enter clinical development eventually makes it to the market as a drug, underscores this uncertainty.

This scientific difficulty is even more pronounced when it comes to medical products aimed at thwarting bioterrorism pathogens. (Notable exceptions may be vaccines against anthrax and smallpox and even pandemic flu because of the wide body of scientific knowledge about both pathogens and the regulatory experience with approved, successful vaccines.)

The reasons why biodefense products are more difficult to produce are straightforward. First and foremost, vaccines and new drugs designed to thwart bioweapons cannot be tested for effectiveness in human field trials as products for control of naturally occurring diseases are. These bioterrorism pathogens, at least in the weaponized forms, don't exist in nature so efficacy must be proven in animal models and then bridged to clinical studies. This regulatory process was established by the FDA in 2002 but is not as well developed or as familiar to regulators. That can create regulatory roadblocks, especially for pathogens for which there are no existing medical countermeasures.

The Standard Drug Approval Process

To see how the process for developing biodefense products can be scientifically more complicated, it is important to have a firm understanding of the traditional drug development process. Most new drugs must go through preclinical testing, and then the familiar three phases of clinical trials. After a drug developer discovers an active molecule that it believes will make a good drug, the developer will continue to perform a long series of laboratory experiments on the molecule. First, it wants to fully gauge the new molecule's effect on normal and diseased cells, usually in animals and in Petri dishes, to see if the new drug or vaccine is effective against cellular and tissue cultures or "assays" that can mimic human organs and even human diseases. In addition, the drug developer will want to make sure its new drug does not have any obvious safety problems, and will also be "druggable"—meaning that it can get absorbed by the body and reach its target organ in order to have its desired effect. In the case of vaccines the objective is to confirm that the immune response effectively blocks the disease process. All of this is considered "pre-clinical" work, and it can take as many as five years to complete, and in exceptional cases, even longer. Yet the process of developing the molecule into a safe and effective drug or vaccine has barely begun. If the pre-clinical testing continues to demonstrate that the new drug may be effective, and if no serious signs of safety problems have emerged, only then can the drug be tested in people. The drug developer will file an Investigational New Drug Application with the Food and Drug Administration, asking the agency to let the drug developer begin human testing.

This begins the familiar three phases of clinical trials that most new drugs must complete. The first step is phase I trials. In phase I trials the new molecule is given to people, often for the first time. Up until now, the drug has only been tested in lab animals. Phase I trials are focused on determining whether the new molecule has any obvious safety problems. The drug's developer, and the FDA, is less concerned with proving whether or not the drug works than in proving it will not cause patients to have serious and/or immediate side effects. If the data from the phase I trial all points in a positive direction, if no serious safety concerns have emerged, and if the drug's developer is still committed to the compound, then the drug is permitted to move on to phase II testing. People in the phase II trials are usually assigned at random to either the investigational group, which is given the new molecule, or the control group, which receives the standard of care and/or a placebo in place of the new, active molecule. Usually, neither the participants in the trial nor their doctors choose which group individual people will be in, the placebo group or the active molecule group. This is what "blinding" means. The addition of the sugar pill or vaccine lacking the disease specific molecule makes this a "placebo-controlled" trial.

In the phase II trial, the drug developer and the FDA are continuing to collect information about the safety and effectiveness of the new molecule. The phase II

trial is also the point at which the optimal dose of the new drug is going to be established. At this point in the clinical development process, endpoints are also established that will be used in the next trial, and will serve as the benchmark for measuring whether people are benefiting from the new drug. Perhaps most important, in the phase II trial, the new molecule needs to start showing that it may be an effective drug if the drug's developer and the FDA, are going to allow the molecule to progress on to the phase III clinical trials. The goals of the phase III trials are to confirm the effectiveness of the new drug against the medical condition that it targets, based on the statistical end points set in the phase II trial. The phase III trial also continues to build information to support the safety of the new compound for its intended purpose. Scientists will use the phase III trial to carefully probe for any possible side effects that may have been hinted at in some of the earlier trials, as well as try and assess the new molecules safety in longer-term use.

Phase III clinical trials are usually tightly controlled, double blinded studies. That means that neither the patient nor the doctor knows who is getting the active drug and who is getting a placebo. The active molecule will typically be tested on at least 1,000 patients, and cardiovascular trials and especially vaccine trials can include 50,000 patients or more. In the end determining effectiveness is a relatively simple matter of showing that significantly less disease occurs in people receiving the active molecule than in those receiving the placebo. Understandably, these trials are expensive, and the cost rises with the number of patients included in the trial as well as the amount of testing that each patient undergoes. So if patients need sophisticated blood tests or imaging scans to monitor their progress while on the drug (this kind of testing is becoming routine and is often required) costs can increase significantly. The total cost for a phase III trial can range in cost from tens of millions of dollars, to hundreds of millions. One recent phase III trial, for a cardiovascular drug developed by pharmaceutical company Pfizer, is estimated to have cost about \$800 million.

If the new molecule is demonstrated to be safe and effective for its intended use in two large, rigorous, phase III studies, then the drug is usually deemed successful and suitable for approval by the FDA.

The Approval Process for Biodefense

This is the standard approval process for drugs and vaccines that can be tested in people against diseases commonly found in the population. The difficulty of carrying out this development process increases significantly when rare and highly deadly infectious agents are involved, especially agents that are not found in man and could never be safely or ethically introduced into people for the purposes of testing a new drug. This includes almost the full panoply of agents that are feared to be the preferred weapons of would-be bioterrorists, pathogens such as anthrax, smallpox, inhaled tularemia, and Ebola virus, among others.

As a result, developing medical countermeasures to these pathogens requires that drugs and vaccines targeted against them need to be extensively tested in animals that can most closely approximate humans, typically large primates. The regulatory pathway inside the FDA that makes this kind of approval process possible for Biodefense agents is commonly referred to as the animal rule.^{22 23}

The animal rule was intended to offset the regulatory difficulty of approving biodefense products, and it does—to a point. While this process accelerates the testing of drugs to treat bioterrorism pathogens, and while efficacy in animals has been shown to closely approximate effectiveness in humans, regulators remain skittish about approving a product based solely on efficacy in animals. All of the available data shows that medical products that have unique development pathways face higher regulatory hurdles and more uncertainty in their development process than those that follow familiar patterns, often times owing to the FDA's unfamiliarity and/or discomfort with these approval pathways.

The development pathway for biodefense products, and especially those that rely on animal efficacy data, is no exception to this general rule. Biodefense products have perhaps the least well-traveled development pathways and the most uncertain requirements from a regulatory standpoint. In addition, the fast development and delivery cycles envisioned by BioShield and necessitated by national security needs add further challenges to this market. As an example, the new anthrax vaccine development process will create a completely novel blueprint for other products coming out of BioShield, one marked by an accelerated process for development and delivery of a therapeutic process. Finally, testing drugs and vaccines in large primates is no small feat. First, it is extremely expensive. In addition, deadly diseases such as those noted cannot be tested in ordinary settings—they require high security laboratories, of which there are a limited number in the U.S. The kind of facilities that this development work requires, and security measures, adds to the time and cost for development.

All of these elements make biodefense drug research unusually risky for investors and drug developers. Indeed, the further one gets from traditional disease and drug markets, the more the rules that investors, and drug developers, have become accustomed to no longer apply. As a result, investors and drug developers have no financial, marketplace, and scientific guideposts on which to orient their endeavors into biodefense drug development.²⁴ To overcome the uncertainty of investments that have higher risk, they demand that these investments also come with higher potential returns.²⁵ In biodefense, more robust profit margins for successful products is unlikely given the public procurement process these products must depend on.

Political Uncertainty also weighs on Development Efforts

But the problems with biodefense drug development do not stem merely from the serendipity of science, marketplace failures, or fickle regulation. Many of the

most significant problems are man made—stemming from the machinations of our political process. Recent intrusions into the scientific process for contracting and procuring biodefense products add another layer of uncertainty to this therapeutic area, a layer of political risk. Political risk is not unique to bioterrorism products. It also weighs on other therapeutic areas. But in every case, political uncertainty has harmful public health consequences. Where political uncertainty weighs most heavily on the prospects for a successful drug launch, drug developers tend to avoid substantial new investments in research.

The market for development of new drugs that target HIV/AIDS provides perhaps the most instructive example of the potential impact of political and economic uncertainty on development efforts. While there is still ample private research into new AIDS medicines, and there are promising therapies in the pipeline, many of the biggest pharmaceutical companies have scaled back the investments they once made in this therapeutic area, in lieu of other unmet medical needs with equal or better payoffs and less political risk—therapeutic areas such as cancer, Alzheimer's and heart disease.²⁶

While a number of big drug makers are still working on new targets as well as better versions of drugs that are aimed at the same parts of HIV as our current crop of medicines, a survey of the 28 HIV drugs in development that are aimed against completely new targets inside the virus find that small biotech companies discovered or are developing 23 of them.²⁷ Another survey of pipeline data found that there are 30 drugs in development that directly target the HIV virus. About 1.1 million people living in the United States are HIV-positive, although that figure dwarfs the worldwide burden of disease, which some estimates place in the hundreds of millions. By comparison, there are 37 drugs in development for skin cancer, most aimed at melanoma. There are 1 million new cases of skin cancer diagnosed in the U.S. each year, only 53,600 of which are cases of melanoma. Admittedly, HIV is a therapeutic area crowded with effective therapies while melanoma remains a largely unmet medical challenge. But if one were appropriating development dollars based solely on market opportunity and burden of disease, HIV/AIDS should still garner a higher share than melanoma, and certainly not less development effort.

What explains the discrepancy? Pharmaceutical executives admit that the political risk of developing new HIV medicines weighs heavily on their minds, and it can be inferred, on their business decisions. Big drug companies make big targets, and many of the large pharmaceutical companies that develop HIV medicines have been threatened with compulsory licenses by foreign governments that do not want to pay even markedly reduced prices for these medicines. Because many developed nations have the technical capacity to reverse engineer patented drugs, they are in a strong bargaining position for negotiating price reductions with foreign producers, backed up by the credible threat of compulsory licensing. In 2001 the Brazilian Health Minister used this approach with Roche and Merck for their drugs Nelfinavir and Efavirenz,

eventually negotiating price reductions of 40 to 70%. This tactic was repeated again this year, to exact price cuts from drug makers Gilead Sciences and Abbott.

The impact of politics on drug markets can also be observed in the market for medicines that treat serious mental diseases such as schizophrenia and other forms of psychosis.²⁸ The Pharmaceutical Manufacturers Research Association reports only 13 novel drugs in development for treatment of schizophrenia and only three of these are in advanced stages of clinical development.²⁹ Yet Schizophrenia is estimated to affect about 2 percent of Americans. If the ongoing drug development work does not meet the public health need, what can account for the underinvestment and underdevelopment in the area of schizophrenia? Mental health is already an area of drug development that is marked by an unusual degree of scientific and regulatory risk. In the area of depression, for example, drug developers experience a lot of failed trials, even for compounds that are ultimately demonstrated to be safe and effective. Clinical research in the area of depression and mental health is also unusually expensive, and simply not very advanced. There is a problem with a high placebo effect. For a lot of studies, even when an active, proven substance is being evaluated as the active comparator, that compound can still fail to differentiate or separate from placebo. One reason is that the measures used to determine whether a drug is effective are not advanced. It requires drug developers to recruit large trials in order to tease out small measures of benefit.

Like drugs aimed at HIV/AIDS and biodefense, in addition to comparatively greater scientific risk and development hurdles, there is also a high degree of economic and political risk in developing new treatments for mental health, especially for drugs that treat more serious mental disease.^{30 31 32} Serious mental conditions, such as schizophrenia, which are often treated with newer generations of drugs known as atypical antipsychotics, often become diseases of poverty and low economic achievement, largely owing to the destabilizing effects that these awful diseases have on peoples' lives. This is especially true of the capacity for these diseases to impede peoples' ability to consistently perform well at work, to hold stable jobs, and achieve economic advancement. As a result, the most serious forms of these diseases tend to be heavily represented among the poor and homeless, and in turn, the drugs used to treat them reimbursed by social programs such as Medicaid, which are geared toward providing healthcare benefits to the poor.^{33 34} In 2003, for example, sales of the new antipsychotics totaled \$6.5 billion, according to an estimate by Richard T. Evans, an analyst at Sanford C. Bernstein & Company. About a third of those sales were to state Medicaid programs.³⁵

The impact of exogenous and unique risks on the private drug market can also be seen in other therapeutic areas, where unique burdens increase the uncertainty and therefore the risk level beyond the threshold that most investors and drug development enterprises are willing to tolerate. These include contraception and women's health, where liability risks are particularly prevalent,

as well as vaccine development. Many medical experts say that specific ailments go neglected because of unusually high political barriers, among other impediments, to concerted drug development efforts.³⁶ In short, distribution of returns on research and development for new drugs in these high-risk areas continues to be highly skewed as a result of a variety of factors that spring more from changing political fortunes than changes in science and medicine, or the markets for these products as reflected by consumer demands. This lesson demonstrates that political intrusions can steer drug development work away from areas where the public health needs require more effort.³⁷

Political Risks are Manifold in Bioterrorism Defense

These lessons ring especially true when it comes to biodefense, where additional uncertainty stems from the heavy reliance that product developers have on government procurement, and where the process for developing and marketing a successful biodefense product is subject to political intrusion and shifting standards that are decreed by policy prerogatives rather than more predictable patterns set by the natural ebb and flow of disease and by the broader marketplace. For these reasons, big drug and biotechnology companies largely have shunned the area, and even smaller firms have a hard time financing development programs on the funding available under government contracts, or raising capital in the public or private equity markets given the uncertainty that past political intrusions have cast in the minds of would-be investors.³⁸ Since BioShield has passed, fewer than 100 companies have come forward and said that they have an interest in pursuing countermeasures.

Ironically, when it comes to biodefense, the overlay of political considerations onto the drug development process was articulated in the very legislation intended to stamp out the uncertainty of developing countermeasures for bioterrorism. The original Bioshield reflected the ambivalence of the political process about public sector funding selection of winners and losers in the commercial sector, as well as antipathy toward allowing outsized profits that are necessary to coax investments in high-risk areas like biodefense. One part of the original Bioshield legislation stipulated that products that have non-biodefense applications would be ineligible for Bioshield support. Congress wisely eliminated that prohibition before enacting the final version of the legislation. But the general ambivalence from which this provision sprung colored other provisions of the legislation; especially the incentives offered to successful development efforts.

The conflicts between political and scientific considerations have also impeded the implementation of the Bioshield provisions, inviting criticism from companies that took up the challenge of creating bioterrorism countermeasures. Typical among these were comments made at a recent Congressional hearing by Richard Hollis, chairman and CEO of Hollis-Eden Pharmaceuticals Inc. who complained about bureaucratic delays in contracting for his company's Neumune immune regulating hormone, a potential treatment for acute radiation syndrome.

The small biotech company's shares fell 20 percent on October 1, 2003 following a negative analyst report that cited uncertainty regarding the government's commitment to purchase Neumune. The Department of Defense has approached Hollis-Eden two weeks after the Sept. 11, 2001 attacks with a request to rapidly develop the drug, Hollis said. But over the three and a half years it has attempted to develop Neumune, the biotech company has "witnessed a clear lack of consensus as to what the government wants; how much they will buy; what they will spend; when they will buy it; and who is making decisions," Hollis asserted in his testimony.³⁹

In another widely reported experience, Danish biotech company Bavarian Nordic A/S is developing a smallpox vaccine targeted at treating the estimated quarter of the U.S. population that might react adversely to current smallpox vaccines. The company says it received \$20 million of a larger National Institutes of Health contract for research and development after the BioShield law was passed, but then had to spend \$50 million on manufacturing facilities in hopes of securing a large portion of a BioShield contract potentially valued at about \$1 billion. In May, the Department of Health and Human Services announced that the government's firm order will be for just 10 million to 20 million doses—far less than the 60 million doses that Bavarian Nordic had expected. In a recent draft proposal, officials indicated perhaps another 60 million doses would be optional but could be canceled. The company gambled, but the episode underscores how much harder it can be to predict defense procurement needs than consumer demand for a new therapeutic and how hard it is in biodefense to make the same advance capital commitments required for most drug and vaccine production.⁴⁰

A recent *Wall Street Journal* article also traced the effort to create an anthrax vaccine to address one of the most immediate bioterrorism threats.⁴¹ For initial contracts to conduct early-stage research on developing such a vaccine, the National Institutes of Health selected two companies: Avecia Group PLC of the United Kingdom and VaxGen Inc. of Brisbane, Calif. Each received about \$100 million in NIH funding, and became the finalists, competing for a roughly \$1 billion order for the next-generation anthrax vaccine for the national stockpile. A third company, BioPort Corp., which makes an existing vaccine, did not qualify for the bidding because its vaccine is based on previous-generation technology. Last fall, HHS awarded the entire \$878 million for a next-generation recombinant anthrax vaccine to biotechnology company VaxGen.

Immediately, rival BioPort criticized the U.S. government decision to "single source" the whole supply. The complaint came about the same time as the shutdown of a Chiron Corp. influenza vaccine plant left the U.S. with just a single source of flu vaccine to cope with the winter flu season. One letter echoing the complaint, issued by a ranking member of the Senate Finance Committee, called the \$877 million anthrax-vaccine contract to a single company "highly suspect." The letter argued that the flu-vaccine shortage in the United States was a result of the government's reliance on only a few manufacturers. "The country lost half

of its flu vaccine supply when the Chiron facility in England was shut down due to contamination problems. ... It appears that HHS may not have learned a lesson from the recent flu vaccine shortage.” In reality the problems encountered by Chiron in manufacturing a viral vaccine in chicken eggs bear little direct relevance to the manufacture of an anthrax vaccine through bacterial cell culture.

When BioPort’s initial efforts failed to change HHS’ decision, they simply increased their lobbying efforts and expenditures, demonstrating the vulnerability that these procurement decisions have to political considerations.^{42 43 44} BioPort eventually did get a contract to supply five million doses of the vaccine to the stockpile, but HHS officials delayed making the purchase, setting off additional complaints on Capitol Hill. Ironically, the logic used to attack the single source contract may reveal the benefits rather than the shortcomings of such an approach. Having one company produce all 75 million doses of anthrax vaccine will cut contracting costs, since the cost of vaccine manufacturing traditionally falls with greater production scale. Having a single supplier also eases distribution in the event of an attack and eliminates the need to prove that different vaccines are interchangeable. Right now, more than half (17 out of 31) of the FDA-licensed vaccines in the U.S. have a single commercial manufacturer. VaxGen maintains publicly that the distraction caused by BioPort's complaints raised the cost of new capital the company needed to continue production.⁴⁵

When allocating resources to any therapeutic area, pharmaceutical and biotechnology companies conduct sophisticated portfolio analyses to try and determine the anticipated costs and the expected return.^{46 47} While public health priorities weigh on these decisions, there are only a finite number of high-risk areas to which companies can allocate their limited resources especially in the face of less than certain returns. The overarching goal of portfolio strategies is to maximize the expected economic returns at an acceptable level of risk for a given level of resources in a new product development pipeline.

Large and well capitalized companies can afford to address some public health priorities where the rewards are likely to be low but the societal need is high. But while therapeutic areas like HIV/AIDS may take priority over some other investment decisions that offer better returns, the public markets require that the bulk of investment capital needs to be allocated to the biggest potential markets, with the most stable development pathways and the most predictable returns.⁴⁸ This is why so much investment is focused on therapeutic areas like heart disease, cancer, and neurodegenerative diseases. Development pathways are relatively stable and clear in these diseases, the cost of development is predictable, and the market opportunity can be readily estimated. Moreover, reimbursement patterns are established and the risk of political intrusion into drug development in these areas—owing to the high therapeutic need—comparatively low.

The same cannot be said of therapeutic areas like HIV/AIDS or even psychosis, and now biodefense and this truth can weigh heavily on the minds of companies contemplating significant development in these areas. This is one reason why investments in these areas are declining relative to development efforts undertaken in other therapeutic niches, despite a growing population of HIV/AIDS patients and people suffering from serious mental illness, and an overwhelming public health need in all of these therapeutic areas.

Conclusion

Indeed, the market for developing medical countermeasures for bioterrorism always fit perfectly the same mold that challenged drug and vaccine development in areas like HIV/AIDS, among others. These challenges include higher scientific and development risk, coupled with higher political uncertainty. In fact, by most measures, developing therapeutic products for biodefense is fraught with more scientific difficulty than most disease areas, especially given the ambitious development timelines envisioned by BioShield. Is it any wonder that investors and drug developers have been reluctant to enter this new market?

While BioShield has mitigated some of these risks, the financial provisions of the legislation have not been enough, so far, to fully offset this unusually high degree of risk and uncertainty for most would-be drug and vaccine developers. And recent events, such as those experienced by Bavarian Nordic, Hollis-Eden Pharmaceuticals, and VaxGen, only reinforce the prevailing view that the market for biodefense is fraught with unusually high development hurdles and political risks, unlike any other therapeutic area. This does not bode well for a future filled with an increasing number of biological threats, the expertise to harness it, and the willingness to use them as weapons of terrorist war.

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