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Incentives for Biodefense Countermeasure Development

Jason Matheny, Michael Mair, Andrew Mulcahy, and Bradley T. Smith

Therapeutics and vaccines are available for only a fraction of biological threats, leaving populations vulnerable to attacks involving biological weapons. Existing U.S. policies to accelerate commercial development of biodefense products have thus far induced insufficient investment by the biopharmaceutical industry. In this article, we examine the technical, regulatory, and market risks associated with countermeasure development and review existing and proposed federal incentives to increase industrial investment. We conclude with several recommendations. To increase industry's engagement in biodefense countermeasure development, Congress should expand BioShield funding, giving HHS the flexibility to fund a portfolio of biodefense countermeasures whose revenues are comparable to those of commercial drugs. Congress should establish tradable priority review vouchers for developers of new countermeasures. A National Academy of Sciences or National Biodefense Science Board should formally evaluate incentive programs and a government-managed "Virtual Pharma," in which HHS contracts separate stages of research, development, and production to individual firms.

Biodefense planning by the U.S. government emphasizes the use of medical countermeasures, including drugs and vaccines, to prepare for and respond to attacks involving biological weapons.[1–4] Currently, medical countermeasures are available for only a fraction of biological threats, including those representing the highest risk, as determined by the Department of Homeland Security's (DHS) threat assessments.[2] It is generally acknowledged that incentives of the scale and structure needed to motivate the biopharmaceutical industry sufficiently to invest in countermeasure research and development (R&D) have been lacking.[5–7] Although federal investment in countermeasure R&D has increased since 2001,[8] few private pharmaceutical and biotechnology companies are engaged in countermeasure development, fewer have advanced candidates through clinical trials, and fewer still are likely to market products.[9] Out of 11 requests for proposals issued by the Department of Health and Human Services (HHS) for biodefense countermeasures, only six products have been procured—none from a large pharmaceutical firm.[10]

In this article, we discuss the challenges to industrial investment in countermeasure development, review existing and proposed federal incentives for countermeasure R&D, and recommend measures to increase industry's engagement in the medical countermeasure enterprise.

Commercial Pharmaceutical R&D: Lengthy, Costly, Risky

Pharmaceutical R&D is a lengthy, costly, and risky process (Table 1). The transformation of a promising drug candidate into a marketable product typically takes 10 to 15 years from basic research to Food and Drug Administration (FDA) approval.[13] The cost of R&D for a single product, including the cost of capital and the cost of failures, is in the

Jason Matheny, MPH, MBA, is a Consultant; Michael Mair, MPH, is an Associate; and Bradley T. Smith, PhD, is a Senior Associate; all are at the Center for Biosecurity of the University of Pittsburgh Medical Center, Baltimore, Maryland. At the time this article was written, Andrew Mulcahy, MPP, was an intern at the Center for Biosecurity of UPMC; he is currently a doctoral student, Health Care Systems Department, Wharton School, University of Pennsylvania, Philadelphia.

hundreds of millions of dollars. One commonly cited estimate of the mean R&D cost per new drug (including the cost of failures and the cost of capital) was $800 million in 1997; current costs are likely to exceed $1 billion per drug.[11,13] Between five[12] and nine[14] drug candidates enter clinical trials for every one approved by the FDA. Even drugs that reach market may not generate enough revenues to cover costs.[15] Thus, the profitability of a pharmaceutical company depends on a small number of blockbuster drugs.

In markets for traditional drugs (e.g., those that address cholesterol, diabetes, or cancer), drug developers can estimate demand, price, and expected return on R&D investments from data on disease prevalence, willingness-to-pay, and market competition. A developer decides to move forward with a project when its expected profits are higher than those of any other possible project.[16] Absent other incentives, developers will invest in R&D for mainstream products with which they have prior experience and that possess a broad, well-defined market, clear clinical research goals, and an established path to regulatory approval. These characteristics are scarce in the anti-infectives market and virtually absent in the biodefense countermeasures market.

Why Anti-infectives Are Unattractive to the Pharmaceutical Industry

Anti-infectives include all therapeutics and vaccines that treat or prevent infectious diseases. In 2004, among the world's 15 largest pharmaceutical companies, only 10% of publicly disclosed New Molecular Entities were classified as anti-infectives.[17] Anti-infectives are generally a low priority in pharmaceutical R&D because of technical, regulatory, and market risks. Developers see high financial returns in targeting chronic diseases that offer repeated sales, while infectious diseases are typically acute in developed countries (HIV being a notable exception).

From 1998 to 2002, FDA approval of new antibacterial agents decreased by 56%, compared with the period 1983 to 1987.[17] Between 1998 and 2004, only two antibacterials were approved that had novel mechanisms.[17] Most major pharmaceutical companies have left the antibacterial market because of increased regulatory risk, shrinking margins, and a short drug life cycle due to bacterial resistance.[18–20] By one estimate, a fourfold increase in antibacterial R&D effort would be needed to generate just one novel-mechanism antibacterial by 2012.[21]

The number of pharmaceutical companies producing vaccines has decreased from 26 in 1967 to 17 in 1980, to 5 in 2004.[22] Among these five companies, vaccines generate less than 10% of their total revenue.[22] Investments in vaccine R&D are generally unattractive to industry for several reasons:

- Vaccines are generally used only a few times in a lifetime and thus generate low expected revenues;
- By reducing disease transmission in a population, vaccines provide broad benefits for which vaccine producers are not fully compensated;[23]
- Large government purchases lead to low margins;

Table 1. R&D Process for a Typical New Drug

		Clinical trials				
Stage	Discovery/ preclinical testing	Phase I	Phase II	Phase III	FDA	Phase IV
Years	6.5	1.5	2	3.5	1.5	Additional post-marketing testing required by FDA
Test population	Laboratory and animal studies	20–100 healthy volunteers	100–500 patient volunteers	1,000–5,000 patient volunteers	Review process/ approval	
Purpose	Assess safety, biological activity, and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Evaluate effectiveness, monitor adverse reactions from long-term use		
Capitalized costs ($M, range)	335–381	467–487				
Success Rate	5,000 compounds evaluated	5 enter trials				

Source: Adapted from Adams[11] and Pharmaceutical Research and Manufacturers of America (PhRMA).[12]

- Since vaccines are given to healthy people, they face higher regulatory requirements and litigation risks;[22,24,25]
- For vaccines and other biologics, the FDA requires that companies begin building physical manufacturing capacity prior to product approval;[26]
- The probabilities of success at each R&D stage are lower for vaccines than for many other pharmaceuticals;[27,28] and
- The basic research pipeline for vaccines is small: between 2000 and 2005, only 3% of NIH grants included "vaccine" as a keyword.[29]

Why Biodefense Countermeasure Development Is Unattractive to the Pharmaceutical Industry

Virtually all biodefense countermeasures are anti-infectives and, as such, face the general challenges described above, as well as risks peculiar to biodefense.

Clinical trials cannot be used to assess the efficacy of most biodefense countermeasures against rare and lethal pathogens. There are few, if any, naturally occurring cases of most of these diseases in humans, and it is unethical to infect a person with a potentially lethal pathogen.

While safety must be shown in humans, the FDA's Animal Efficacy Rule establishes a pathway for countermeasures to be proven effective using validated animal models.[30] However, for many biodefense diseases of concern, animal models have yet to be developed and validated. Moreover, animal models represent, at best, a rough approximation of efficacy in humans, and, as such, countermeasures developed using animal models will be untested until their use in humans during an emergency.[31]

The FDA has yet to release comprehensive guidance on the Animal Efficacy Rule, and no novel products have been approved using the Rule; the Rule has thus far been used to extend the indicated use of previously licensed products.* Emergency use of a countermeasure that is in late-stage development but has not yet been approved by the FDA is possible through the Emergency Use Authorization (EUA) provision under the BioShield legislation.[32] Currently, the FDA is expected to require extensive safety and efficacy data prior to granting a product EUA status. However, it is unclear what standards for safety and efficacy will qualify some products and disqualify others—and the determination is made during, not before, an emergency.

The scope, magnitude, and type of a future biological attack is uncertain, as is the demand for countermeasures.[33] Because the response to a major biological incident will be coordinated by governments, government purchases will be the major (if not the only) sale for most countermeasures. (At present, the U.S. government is by far the largest purchaser of biodefense countermeasures.) Countermeasure developers must thus rely on governments to determine and communicate the market for biodefense countermeasures. But government purchasing is subject to evolving threat assessments and shifting political priorities, which create market uncertainties.

Developers' dependence on government purchases presents additional problems. A government has every incentive to negotiate prices for countermeasures just above their marginal cost of production, thus severely limiting profits. If companies resist low prices, governments can, in extreme cases, threaten compulsory licensing or purchase patent-breaching generics. In 2001, following the first anthrax attacks, the U.S. government threatened such actions during negotiations with Bayer over its antibiotic, Cipro. The threat was credible, and Bayer lowered its (already wholesale) price for the drug.[34] When a developer's R&D costs are already spent, the best a developer can do in such cases is accept the government price. The prospect of a hard bargain causes drug developers to be wary of developing products whose prices are not guaranteed to cover R&D costs.

The technical, regulatory, and market risks associated with biodefense countermeasures lead to weak commercial investment and thus few products. Given companies' fiduciary responsibility to investors, even countermeasures that are profitable at the margin will be ignored as long as companies can focus their investments on more profitable products.

Existing Incentives for Biodefense Countermeasure R&D

Given the importance of biodefense to national security, the U.S. government has employed a broad menu of financial incentives to spur commercial investment in countermeasure R&D (Table 2). This menu can be separated into "push" incentives, which reduce industry's cost of R&D and are typically used to motivate early-stage research, and "pull" incentives, which increase industry's revenues from R&D and are typically used to motivate late-stage development and production. To date there has been little analysis of the effectiveness of these incentives in accelerating coun-

*Two products have been approved using the Animal Efficacy Rule; both were products previously approved for use in the U.S. or Europe and used the Animal Efficacy Rule only to obtain approval for additional indications. Pyridostigmine bromide for prophylaxis against nerve agents has been approved using the Animal Rule, but this drug had already been approved in 1955 for the treatment of myasthenia gravis. Hydroxocobalamin received an indication for cyanide poisoning as well as smoke inhalation, but it had been approved in France since 1996. It remains to be seen how a genuinely new product will fare under the Animal Efficacy Rule.

Table 2. Incentives for Biodefense Countermeasure R&D

Incentive Mechanism	*Examples*	*Strengths*	*Weaknesses*
Push Incentives			
Government R&D and technology transfer	NIH/DoD intramural research	Control over research path Open results	Weak financial incentives for performance
Government research grants and contracts	NIH/DoD extramural grants	Self-selection of quality researchers Open results	Difficult to judge value of applications
Government-industry R&D collaborations	CRADA	Avoids duplication of infrastructure	Complicated IP environment
Liability protection	Safety Act PREP Act	Reduces developers' risks	Potential to reduce safety
Tax credits	Standard R&D tax credit Orphan drug tax credit	R&D may be more efficient than average tax spending	Less attractive to companies with low profits
Pull Incentives			
Regulatory rewards	Priority Review designation	Reduces time to market	Increased FDA costs
Exclusivity reward	Patent protection Orphan drug market exclusivity Pediatric exclusivity provision	Valuable industry	Limited value for products with small markets Reduces competition on price and quality
Procurement contracts	DoD procurement HHS procurement (e.g., BioShield)	Bidding promotes cost control Familiar to government No duplicate costs	Difficult to predict success of winning bidder Contract must be adequately specified

termeasure development. A range of existing and possible incentives are discussed below.

Push Incentives Used for Biodefense Countermeasure R&D

Government R&D and technology transfer

HHS and the Department of Defense (DoD) conduct in-house (intramural) basic R&D focused on biodefense countermeasure development. Discoveries produced by federal scientists conducting basic R&D are often made available to the private sector through publication in scientific literature, or they may be patented by the federal government and made available to the private sector through technology transfers. Examples of biodefense-related technology transfers include the AVA and rPA vaccines for anthrax, which were initially developed by DoD and licensed to BioPort (now Emergent) and VaxGen, respectively. Government R&D allows government managers to retain control over the direction of research, but it does not provide them with the financial incentives common in private firms to motivate performance. It is not clear, however, that the lack of financial incentives leads to a lower rate of success or to reduced efficiency; the cost-effectiveness of government-managed drug development projects, such as that at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), appears not to have been evaluated.

Government research grants and contracts

HHS, DoD, and, to a lesser extent, DHS award research grants to institutions for countermeasure development. Most grants for research in biodefense are awarded by HHS through the National Institute of Allergy and Infectious Diseases (NIAID).[35] In FY2006, NIAID awarded $1.7 billion in funding for biodefense-related research.[8]

On December 19, 2006, President Bush signed the Pandemic and All-Hazards Preparedness Act into law (P.L. 109-417), which created the Biomedical Advanced Research and Development Authority (BARDA) within HHS. One of the purposes of BARDA is to fund the development of products across the so-called "valley of death" between NIAID-funded basic research and end-stage procurement by the BioShield program (described below). Recipients of government grants and contracts are motivated to use funds judiciously, as evaluations of their results are typically used in future grant and contract reviews. But it can be difficult for reviewers to accurately judge the value of a project based solely on an application or bid, and the application process is slow: The NIH R01 grant review process, for instance, takes 9 months, on average, from application to award.[36]

Government R&D collaborations

Collaborations allow government, academia, and industry to share scientists, materials, facilities, and other resources. Over the past 3 years, NIH has entered into about 250 Cooperative Research and Development Agreements (CRADAs).[37] A 2005 CRADA teamed MedImmune researchers with government scientists in NIH laboratories to develop vaccines against pandemic influenza strains. USAMRIID has entered into CRADAs to develop anthrax therapeutics. NIAID makes several of its resources available to industry, including a program to screen drug candidates against biological agents.[38] By sharing resources, CRADAs reduce the duplication of equipment and space, thus reducing R&D costs. The chief disadvantage of CRADAs is that technologies resulting from joint public-private research face complicated disputes over intellectual property.

Liability protection

Liability protection reduces the financial risks to developers by lowering the costs of possible litigation. The first use of a medical countermeasure may be during an emergency, when the product is given to a large number of people. The potential for unforeseen side effects is significant. Liability protection can be made available to countermeasure developers under the SAFETY Act (part of the 2002 Homeland Security Act, P.L. 107-296) and under the Public Readiness and Emergency Preparedness (PREP) Act (part of the 2006 DoD Appropriations Act, P.L. 109-148).

R&D tax credits

R&D tax credits allow developers to write off R&D expenditures against their taxable profits in the year the expenditures were made. Government pays the costs of tax credits through reduced tax revenues. From studies in other industries, a dollar in tax credit stimulates a dollar of additional R&D.[39,40] This is efficient when a dollar in tax revenues would not be used as cost-effectively, on average, as a dollar in R&D. Arguably, countermeasure R&D represents such a case. Most companies receive an R&D tax credit equal to around 20% of qualified research expenses. Companies with drugs in development that prevent or treat diseases with a natural prevalence less than 0.05% can be given Orphan Drug Designation (ODD) by the FDA and receive a 50% tax credit on clinical trial expenses. Most if not all biodefense countermeasures should be eligible for ODD.

Pull Incentives Used for Biodefense Countermeasure R&D

Regulatory rewards

Regulatory rewards increase revenues by shortening a product's time-to-market. The average FDA review process for a standard new drug takes 18 months.[41] New drugs thought to offer a significant improvement over existing products qualify for "priority review" status, which shortens the average review period to 6 months.[41] This review, however, comes at some cost to the FDA. The additional FDA labor needed to provide priority review has been estimated at $1 million per product.[41,42]

Exclusivity rewards

Exclusivity rewards allow developers to increase their revenues by reducing competition. The most common exclusivity reward is patent protection. Patents allow developers to hold a time-limited monopoly on, and thus charge a high price for, a novel technology. Patents generally last 20 years, but much of this time is consumed by R&D. Companies with drugs that have been given ODD receive a 7-year market exclusivity period for the orphan indication, which prevents competition from even chemically distinct products for the same indication, as long as the latter are not therapeutically superior. The value of patent and market exclusivity rewards is limited for products that have small markets: Extending a monopoly on an unprofitable product is still unprofitable.[43] These rewards are thus unlikely to be a strong incentive for most biodefense countermeasures, which will be sold only to government(s). However, exclusivity rewards could be valuable for some broad-spectrum anti-infectives that are effective against both biological weapons and more common infectious diseases.

Procurement contracts

Procurement contracts allow developers to earn revenues from developing and manufacturing countermeasures. HHS purchases countermeasures using the Special Reserve Fund created under the 2004 Project BioShield Act, which authorized $5.6 billion over 10 years for procurement, thereby avoiding the uncertainty of the annual appropriations process. Under BioShield, the federal government can sign purchase agreements with companies whose products are expected to be eligible for approval or licensing within 8 years. The federal government pays only upon delivery of the product. The 2006 Pandemic and All-Hazards Preparedness Act allows HHS to make multiple milestone-based advanced payments (up to 50% of the total contract) under BioShield awards, thus allowing manufacturers to earn revenues from developing and manufacturing countermeasures prior to delivery of the product. The Act also gives HHS the authority to contract with a developer to establish "warm base" manufacturing capacity for a countermeasure. To date, six products have been procured under BioShield at a total cost of $1.45 billion.

Procurement contracts are commonly used in government purchases. Competitively bid contracts increase efficiency when the government can accurately assess a firm's prospects for successfully delivering a high-quality product. These assessments are likely to be more accurate in tradi-

tional defense contracting, where developers have a long history of government contracts, than in biodefense contracting, where developers are often new companies developing pharmaceutical products with a low probability of success.

Potential Incentives for Biodefense Countermeasure R&D

Given the threat of bioterrorism and natural epidemics, and the relatively limited commercial investment in countermeasure development, HHS should explore additional R&D incentives that have been used in, or proposed for, other technology initiatives (Table 3).

New Grant Incentives

The immediate threat posed by biological weapons and the long development times required to produce a useable product warrant a faster NIH grant review process. The BioShield Act of 2004 granted NIAID expedited review authority for grants that are clearly biodefense-related.[10] But because biodefense depends on advances made in many biomedical disciplines, the entire NIH grant review process should be accelerated. Alternatives to traditional reviews exist and others have been proposed, including allocating a portion of the NIH funding to be managed by entrepreneurial program managers who seek out opportunities, rapidly fund promising research, then work closely with the scientists to monitor progress.[44] This process has been used with great success by the Defense Advanced Research Projects Agency (DARPA). Others have suggested creating NIH "prediction markets," in which a large community of reviewers can quickly place bets on which research projects will be most productive.[45–48]

Reward Vouchers

Developers have expressed interest in making regulatory or exclusivity rewards transferable across products, in the form of vouchers (also called "wild cards").[6] A developer that successfully produced a countermeasure could be rewarded by being granted a patent extension, market exclusivity, or priority review for any other product in its portfolio, increasing that product's revenues. Vouchers could also be made tradable, allowing one developer to sell its voucher to another developer.

Patent extension and market exclusivity vouchers would increase developers' revenues by delaying the introduction of competition.[15] These would be highly valuable to developers with blockbuster drugs but could be costly to society by delaying the introduction of generics, thus boosting drug prices. Concerns over the costs of these incentives made them unpopular during Congressional debates on BioShield and BARDA.[49]

In contrast, priority review vouchers could be highly valuable to developers without imposing social costs. As explained above, priority review reduces a product's time to market by a year. At the same time, priority review does not delay the introduction of generics, and consumers have access to new medicines a year sooner. A priority review voucher that is *tradable* between developers would allow a biotech firm that successfully develops a countermeasure to sell its voucher to a pharmaceutical firm that has a potential blockbuster entering FDA review. There is risk to a firm in buying a priority review voucher: There is no guarantee that the product to which a voucher is applied will be ap-

Table 3. Proposed Incentives for Biodefense Countermeasure R&D

Incentive Mechanism	*Examples*	*Strengths*	*Weaknesses*
Exclusivity reward	Roaming patent extensions	Valuable to industry	Patent extensions and market exclusivity have high social costs
Regulatory reward	Priority review vouchers	Valuable to industry Priority review vouchers could be highly cost-effective	Voucher could be applied to product that does not become commercially successful
Prizes	DARPA Grand Challenge NASA Centennial Challenges InnoCentive Challenges	No direct payment for failure Defers costs to future	Optimal prize amount hard to determine Need to specify rules and product characteristics in detail Sponsor may default Duplicate research
Advance market commitment	Pilot AMC for pneumococcal vaccine	No direct payment for failure Defers costs to future Market induces competition on quality and price	Optimal AMC size unknown Need to specify rules and product characteristics in detail Sponsor may default Duplicate research

proved by the FDA or become a commercial success. But most products that successfully navigate the clinical trials process and are submitted to FDA for final review are approved, and the risk of failure is likely to be outweighed by the voucher's value: One study estimated a value greater than $300 million when transferred to a blockbuster drug (most of which do not already receive priority review).[41,42] To prevent delayed reviews of medically important products, FDA would need to hire additional staff to review voucher recipients' products. The cost of this additional labor has been estimated at $1 million per product and could be billed to the voucher recipient.[41,42]

Tax credits also could be made tradable. Tax credits are little incentive for the many biopharma firms that are not profitable. However, credits could be made tradable across developers: Unprofitable firms could sell their credits to profitable companies. Alternatively, tax credits could be made deferrable to a future time when a firm is profitable.

Prizes

"First-past-the-post" prizes offer rewards to the first researcher to complete a given research task. "Best entry" prizes reward whichever entry produces the most promising result within a fixed period. Historically, prizes have motivated inventions such as the Harrison Clock, steam locomotion, and photography.[50] They became less common in the 20th century but have enjoyed a resurgence in the past few years. (Patents are, in effect, a "first-past-the-post" prize, where the award is a time-limited monopoly.)

Modern prizes include the DARPA Challenge, the National Academy of Engineering's Grainger Challenge, NASA's Centennial Challenges, the Ansari X-Prize, and InnoCentive's prizes for inventions in chemistry and the life sciences. These prizes offer cash rewards to inventors who develop technologies meeting pre-established specifications. The FY2006 Science, State, Justice, Commerce and Related Agencies Appropriations Act (P.L. 109-108) directed the National Science Foundation to establish a prize program. And in 2007, a National Academy of Sciences committee proposed a program of experimental prizes and evaluations that would offer cash rewards for inventions of public value, under an Office of Innovation Prizes within the National Science Foundation.[50]

One study concluded that a prize is theoretically the best mechanism for eliciting innovation, "if the size of the prize can be linked to the social value" of the innovation.[51] Setting the prize's size is critical, as one can underpay and not motivate any R&D effort, or overpay and waste funds that could have been spent on other priorities. Other weaknesses of prizes are: competing developers will duplicate costs, and sponsors must pay developers a premium to compensate for the risks of default, failure, and competition. The strengths of prizes are: the sponsor pays nothing until a product is successfully developed, the sponsor need not audit or otherwise manage research, and developers will be motivated by competition.

Advance Market Commitments

An advance market commitment (AMC) is a guarantee by a government or other sponsor to pay developers a minimum price per dose of a medical product purchased in the market up to a specified volume.[52] The government issues a detailed set of technical specifications. Products meeting those specifications and purchased in the commercial market are guaranteed a co-payment from the sponsor up to a specified volume of sales. AMCs are distinguished from conventional purchase contracts, as there is a minimum price open to multiple competing developers and no guarantee on the number of doses purchased.

AMCs are untested but have been proposed for tropical diseases, such as malaria, tuberculosis, and HIV; one $1.5 billion AMC has been secured for a (late-development) pneumococcal vaccine.[53] The necessary size of an AMC for a malaria vaccine with one entrant has been estimated at $3 billion—the expected revenues from developing one commercial drug.[52] If a developer expected to split the market with a competitor, the AMC would have to be almost twice as large to spur R&D.

A theoretical model found that combining both an advanced market commitment and a payment of a fixed fraction of the developer's R&D costs is more cost-effective than either incentive independently.[43] Others have similarly recommended that AMCs be combined with milestone payments that provide financial support to companies while they are developing a product.[54]

The strengths and weaknesses of AMCs are like those of prizes.[55] One advantage of AMCs over prizes is that in markets with multiple purchasers, several products can be introduced that compete for market share. However, it is unlikely that the market for biodefense countermeasures will have many purchasers.

RECOMMENDATIONS

Given the urgency of biological threats and the need to engage both large and small biopharmaceutical companies in developing countermeasures, we recommend the following:

1. Congress should expand BioShield funding, giving HHS the flexibility to fund a portfolio of biodefense countermeasures whose revenues are comparable to those of commercial drugs.

To date, the incentives used to promote countermeasure development have succeeded in motivating significant biodefense R&D effort by only a modest number of biotech companies and no large pharmaceutical companies. Project BioShield has been successful in awarding a small

number of contracts for relatively mature products.[10] The first and largest BioShield contract—$877 million for anthrax vaccine—was cancelled in December 2006 because of technical problems with the product and subsequent delays in the development of the vaccine candidate.

BioShield contracts do not resemble the scale and structure of the private drug market. BioShield's effectiveness will always be limited by its funding, which has been insufficient to attract large, profitable pharmaceutical companies. With $5.6 billion to be allocated over 10 years available to purchase countermeasures for at least 14 top priority CBRN threat agents,[2] the expected revenues from developing a countermeasure are significantly lower than the $3 billion or more expected, on average, from developing a single commercial drug.[52] It is not surprising that pharmaceutical companies prefer to chase blockbusters over BioShield contracts. BioShield has so far attracted only small biotechnology companies with lower revenue expectations than large pharmaceutical companies—and limited resources to carry drugs through clinical trials. Perhaps most important, the modest scale of the BioShield fund has prevented HHS from developing a broad portfolio and taking risks with individual contracts. Most products fail in clinical trials; HHS thus needs a budget sufficiently large to fund, in parallel, multiple countermeasure candidates targeting the same threat.

Regardless of how its costs are distributed across society and across time, biopharmaceutical research is expensive, with the average cost of developing one drug around $1 billion.[13] Debate about which incentives are more or less cost-effective than others may be academic when total public investment has to significantly increase—perhaps tenfold—to address existing and foreseeable biological threats. No "funny mirror" incentive exists that can make a $900 million BioShield contract appear as attractive to industry as a $3 billion commercial drug.

Congress has not yet indicated whether additional monies will be added to the BioShield purchase fund once the initial funds are exhausted. This uncertainty complicates management of the fund by HHS and may reduce pharmaceutical companies' investments in R&D for products that will reach maturity after BioShield's expiration.

2. HHS should replicate features of the pharmaceutical market that have succeeded in generating drugs and vaccines of commercial value.

More money is necessary but not sufficient to create a strong biodefense. Success also depends on HHS's ability to create a predictable and well-managed market for countermeasures. The private market has offered sufficient incentives to generate many drugs for chronic diseases such as high cholesterol or acid reflux. For commercial products, developers estimate potential market volume from epidemiologic data and competitive intelligence, and market price from marketing surveys; they anticipate a predictable regulatory process; and they receive push funding from private capital markets and pull funding from repeated sales in consumer markets. HHS can replicate these features of the private market by:

- increasing the detail of price, volume, and product specifications in requests for proposals;
- improving its Tech Watch to identify and fund promising new technologies at early stages;
- clarifying the path for licensure under the Animal Rule and Emergency Use Authorization;
- increasing transparency in procurement decisions;
- providing a mix of push and pull funding, with push funding directed toward early-stage research, and pull funding directed toward late-stage development and production;
- making large volume purchases; and
- shortening the period from when a pathogen is deemed a threat to when a BioShield contract is signed (currently more than 2 years on average).[10,56]

Perhaps most important, HHS can hire managers to lead the government's countermeasure effort who have a history of success in the biopharma industry.[56]

3. Congress should establish tradable priority review vouchers for developers of new countermeasures.

Of the proposed incentives reviewed here, only tradable priority review vouchers have theoretical merits clear enough to warrant immediate implementation. With a potential benefit to industry of $300 million and a public cost of $1 million or less, tradable priority review vouchers would be highly cost-effective.

4. An NAS or NBSB committee should evaluate existing and potential incentives for commercial development of biodefense countermeasures—particularly "flexible" technologies effective against a range of threats.

Despite the billions of federal dollars invested annually in incentives for industrial R&D, few data exist on their cost-effectiveness. HHS should commission a panel of experts from the economic and pharmaceutical development sectors to evaluate incentives for countermeasure R&D. Incentives for other important pharmaceuticals, such as drugs for orphan and neglected diseases, could also be evaluated. This task could be charged to a National Academy of Sci-

ences (NAS) committee or to a working group of the National Biodefense Science Board (NBSB, established by the Pandemic and All-Hazards Preparedness Act in 2006, but not yet constituted).

As biotechnologies become more powerful and more accessible, the range and severity of biological threats will increase.[57] Eventually it will be too slow and costly to stockpile countermeasures for every threat. Two recent U.S. government documents—the White House's Homeland Security Presidential Directive 18 and HHS's Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Strategy—recommend addressing this problem by developing broad-spectrum countermeasures and platform technologies effective against a range of threats. Given this new strategic shift by the government, incentives should be evaluated that can engage academia and industry in the development of these new "flexible biodefense" technologies.[58] As many of these technologies are early-stage, improvements to existing push incentives should be explored.

5. An NAS or NBSB committee should evaluate Virtual Pharma models of government-managed countermeasure development, in which separate stages of research, development, and production are contracted to individual firms.

In principle, government could adopt the "Virtual Pharma" model used by some pharmaceutical companies, in which discrete stages of the R&D process are contracted to separate developers.[59] Under this model, BARDA or a BARDA-like organization could manage a portfolio of products from basic research to production, inviting developers to bid for each step in the R&D process, and tailor the size and structure of incentives accordingly. This model could decrease the costs and risks for both government and developers.

The success of Virtual Pharma depends on the ability of a management team to efficiently contract projects and cancel dead-ends. The experience of Virtual Pharma Public-Private Partnerships (PPPs) in developing drugs for tropical diseases such as malaria, HIV, and tuberculosis suggests that effective management is possible. The R&D costs of PPP projects are significantly lower than pharma's, although their clinical success rates remain to be established.[60,61] It is possible that PPPs gain efficiency by outsourcing R&D to the lowest-cost developers, without regard for potential intellectual property violations or trade secret piracy. Secrecy reduces commercial developers' tolerance for outsourcing, but government-managed programs would not be so constrained.

There is a historical precedent for government successfully managing countermeasure R&D. The greatest period of vaccine discovery was during World War II, when industrial vaccine developers partnered with the lead users of vaccines—the military. Industry scientists reported directly to military managers, who set clear objectives and ambitious schedules for every vaccine and used a combination of push and pull funding.[62] The experience of government-managed countermeasure development should be evaluated and, where appropriate, replicated.

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Address reprint requests to:
Michael Mair, MPH
Associate
Center for Biosecurity of UPMC
621 E. Pratt St., Ste. 210
Baltimore, MD 21202

E-mail: mmair@upmc-biosecurity.org