The difficulty *Nature Biotechnology* encountered in finding accurate information about BioShield and BARDA underlies the communications gap concerning US biodefense. Clearly, what officials at the Office of the Biomedical Advanced Research and Development Authority (OBARDA) are aware of and what information seeps out into the outside world (and to those in industry) are two entirely different things.

The Acambis smallpox vaccine that the FDA's VRBAC acted on in May of this year and approved in September was the live attenuated vaccine (ACAM2000), not the modified vaccinia Ankara as we wrongly stated. We still remain perplexed, however, as to why US officials did not award MVA smallpox vaccine a stockpile supply contract when Acambis already received contracts from the National Institutes of Allergy and Infectious Diseases to develop MVA as a smallpox vaccine for immunocompromised subjects (around 10% of the population). This seems like the right hand not knowing what the left hand is doing. Clearly the decision was a surprise to Acambis; the loss of a potentially billion dollar contract contributed to the departure of the CEO, a 40% slump in share price and a cut in the workforce.

Our description of the Hollis Eden debacle erroneously stated the company had a contract, whereas it only had responded to a Request for Proposal (RFP) for radiation countermeasures. We apologize to our readers and OBARDA for this error. Either contract or RFP, however, the criticism of poor communication by the government still stands.

We also thank Vanderwagen for clarifying the lack of an indemnity clause in the final Pandemic and All-Hazards Preparedness Act—although this means, of course, that BioShield is even less enticing to companies than we originally thought. We still are somewhat in the dark about the indemnity provision in the Emergency Preparedness Act of 2005, which appears to apply only to pandemic flu, part of BARDA's purview. So does the indemnity clause only pertain to part of BARDA's programs?

With regards to the US government's exemption from FOIA under the Act, it seems very likely that officials will find many situations where they regard information must be kept secret if the definition is: "to safeguard non-public technical information deemed to reveal significant vulnerabilities of existing public health defenses, generated during countermeasure or product advanced research and development."

Overall, we remain convinced that the US government needs to do a much better job disseminating information about BioShield and proactively communicating its goals for BARDA and BioShield with companies. Although we welcome the appointment of an interim director, this is hardly the answer to providing clear leadership.

The FDA animal efficacy rule and biodefense

To the editor:

Your editorial in the June issue draws attention to some of the difficulties encountered by companies developing drugs and vaccines under the umbrella of the Bioshield program. We would like to draw attention to one particular impediment to progress—implementation of the US Food and Drug Administration (FDA) Animal Efficacy Rule ('the Rule') to facilitate development of medical countermeasures (that is, medicines and vaccines) for bioterrorism.

The Rule provides a mechanism for licensure when human efficacy challenge-studies are not feasible or ethical, such as for smallpox or anthrax disease, as well as for sporadic emerging infections. As the Rule has been rarely used, questions linger about its implementation. Here, as members of the Alliance for Biosecurity (http://www.allianceforbiosecurity.org/)—a collaboration between the academic, nonprofit Center for Biosecurity of the University of Pittsburgh Medical Center (Baltimore) and drug industry members, including Acambis (Cambridge, UK), Avecia Biotechnology (Manchester, UK), Cangene (Winnipeg, MB, Canada); DOR BioPharma (Miami), Elusys Therapeutics (Pine Brook, NJ, USA), Emergent BioSolutions (Rockville, MD, USA), Human Genome Sciences (Rockville, MD, USA), Iomai Vaccines (Gaithersburg, MD, USA), Pfizer (New York), PharmAthene (Annapolis, MD, USA), Battelle Biomedical Research Center (West Jefferson, OH, USA) and Lovelace Respiratory Research Institute (Albuquerque, NM, USA)—we put forward three major recommendations for facilitating implementation. First, we propose that the Department of Health and Human Services (HHS), the FDA and other US agencies provide strategic direction about how countermeasures may be used; this will aid development and testing. Second, the FDA, along with the National Institute of Allergy and Infectious Diseases (NIAID), should actively develop scientific consensus on animal models for specific disease threats. And finally, the FDA should develop a consistent interpretation of the Rule within the agency.

Effective implementation of the Rule[1] is an urgent priority for biodefense, and yet the Alliance has identified several challenges in its use. From the Alliance's perspective, government, industry and other stakeholders are at a defining moment in the endeavor to identify, create and obtain medical countermeasures that will protect people against bioterrorist attacks and emerging infectious diseases. Development of a medical countermeasure arsenal is a challenging and relatively new responsibility, but we now share six years of experience since the anthrax attacks in 2001.

The FDA and HHS are addressing scientific and regulatory issues for biosecurity, as demonstrated by the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy for Chemical, Biological, Radiological and Nuclear Threats[2]. The strategy notes that HHS will "identify and support critical infrastructure that enables medical countermeasure development such as…animal models." FDA appears to need increased resources to address Rule issues for biodefense countermeasures. We believe that the PHEMCE implementation plan should explicitly address how HHS will assist FDA in accomplishing these goals.

The Rule went into effect under 21 CFR Parts 314 and 601 in July, 2002. Before that time, licensure was not possible for many medical countermeasures that may be needed after a bioterrorist attack, or for emerging diseases that occur sporadically, such as West Nile Virus. Licensure of drugs and vaccines requires extensive testing in humans; it is not possible, for example, to deliberately

infect humans with *Bacillus anthracis* spores to determine whether an anthrax vaccine is protective. The Rule provides the mechanism by which challenge studies can be performed in animal models to show efficacy, thus avoiding the need for efficacy studies in humans.

The Rule does not eliminate testing in humans; clinical trials are still required to evaluate safety of the medical countermeasure and to help determine the appropriate dose. For example, if a company was testing a drug therapy for Ebola virus, humans would be given the drug in clinical trials to determine that the drug is safe. The tests to determine if the drug is efficacious in treating an Ebola infection would be performed in animal models.

Substituting animals for humans in efficacy tests was not intended to make it easier to obtain FDA approval for novel countermeasures. In fact, more information must be known about the animal model itself, the mechanism and course of disease and the mechanism of the countermeasure than when efficacy studies can be performed in humans. Without convincing human efficacy data, it is even more important to thoroughly understand how a countermeasure works, why it works, and to provide data that give reasonable confidence that the countermeasure will be efficacious in humans. For many potential bioterrorism threats, there are no well-characterized animal models available[3], requiring investigators to develop, test and validate animal models, in addition to determining the efficacy and optimal dose of their countermeasures.

Animal models rarely reflect the human disease precisely, so testing in more than one animal species is usually required. The FDA also requires postmarketing human efficacy studies if the countermeasure is used in humans, which would most likely be in the aftermath of a bioterrorist attack. As part of their FDA license applications, companies must therefore develop plans to perform efficacy clinical trials—in the midst of a national crisis.

The novel challenges of the Rule requirements, compared with the traditional licensure pathway, may be one reason it has rarely been used to approve new drugs. The first countermeasure approved was pyridostigmine bromide in 2003, indicated for use after exposure to Soman, a nerve agent[4]. As a different dose of the drug had previously received FDA approval for treating myasthenia gravis, the Rule was not used for a novel compound, but to extend the indicated use of an already existent countermeasure.

The second, recent approval was for hydroxocobalamin, indicated for victims of cyanide terrorism as well as smoke inhalation[5]. This drug had been approved in France in 1996 (ref. 6), and was available in the United States at a much lower dose[7]. However, even though use of the Rule has been rare, new animal models continue to be developed and refined. In the coming years, there will be many completely novel products without human efficacy data applying for licensure under the Rule, which increases the urgency to clarify its implementation.

The Alliance recognizes that the Rule is a novel approach to license medical countermeasures and the lack of animal models for many bioterrorism diseases compounds the difficulty in developing safe, effective medical countermeasures for the strategic national stockpile. Though the Alliance has identified technical, organizational and strategic challenges in implementing the Rule, many of the challenges can be resolved by better and more frequent communication between the stakeholders.

Recommendation 1

First, the HHS Office of Public Health Emergency Medical Countermeasures (OPHEMC), in close collaboration with the FDA and other government agencies, should provide strategic direction to companies that clarifies how needed countermeasures are intended to be used. Although infection patterns for natural infections, such as HIV, are well documented in the scientific literature, the epidemiology of bioterrorism is uncertain, and largely determined by the method of attack. The Alliance recognizes that the goal of the US government is to be prepared to use medical countermeasures for a wide range of scenarios. However, it would help companies developing medical countermeasures to have common planning and testing assumptions, so accurate comparisons can be made between products.

For example, countermeasure development, and application of the Rule, would benefit from strategic guidance from OPHEMC as well as FDA for the following areas.

Population for the countermeasure. A company may develop an animal model for safety and for efficacy that is a surrogate for healthy humans, but which does not model special human populations, such as children, the immunosuppressed or elderly. Companies should receive consistent guidance as to how these populations, as well as the majority population, can best be modeled before licensure.

Exposures that the countermeasure will counteract. In contrast to naturally occurring diseases, a bioterrorist attack could result in a wide range of exposures by different routes, depending upon the method and proximity of the attack. For example, in a scenario mirroring the anthrax attacks of 2001, the person who opens an anthrax-filled letter would likely inhale many more anthrax spores than someone at a distance from where the letter was opened. Both high and low exposures to the spores may be lethal without treatment, but medical countermeasures may be less effective against the higher exposure. Companies should test their products against a common exposure (or range of exposures), specified by the FDA and other government agencies, to allow their products to be accurately compared.

Plans for clinical efficacy studies. If the stockpiled countermeasure is used, clinical trials will be performed to assess its efficacy in humans. Companies are required to submit plans for performing these postmarketing trials along with their government funding proposal applications and for FDA licensure. As there are many possible bioterrorism scenarios for which a stockpiled countermeasure could be used, OPHEMC, FDA and the US Centers for Disease Control and Prevention (CDC) should offer planning guidance to companies preparing these studies.

Multifaceted countermeasures. It may be strategic, and medically important, to have more than one available countermeasure for a given threat. For example, to treat anthrax, it may be strategic to stockpile an antitoxin that could be administered along with an antibiotic. Although the antibiotic may be sufficient therapy, the additional countermeasure may protect in the event of incomplete adherence to the antibiotic regimen, if the *B. anthracis* is antibiotic resistant or if antibiotics are not administered quickly. Similarly, it may be necessary to stockpile a vaccine and an antiviral for a variety of viruses, including smallpox. Direction should be given to companies about whether these kinds of multifaceted approaches are needed for the strategic national stockpile, and the FDA could also give technical advice on how incomplete adherence to antibiotics could be modeled in animals.

Recommendation 2

Second, the FDA, NIAID and other government agencies should decide on acceptable animal models and testing methods

for specific disease threats, with the help of industry. Establishing an acceptable surrogate for human disease will require regular communication among the scientific teams developing animal models. Currently, there are multiple animal model development efforts, such as those in industry; government agencies, especially NIAID, which has a research program dedicated to animal model development[8] and the United States Army Medical Research Institute for Infectious Diseases (USAMRIID); and academia, including the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research. These multiple efforts may be duplicative and fragmented, wasting resources, time and money—and may delay the acquisition of biodefense countermeasures for the strategic national stockpile. To resolve this problem, we propose that the FDA actively engage with industry in a collaboration on the Animal Efficacy Rule. For instance, PDA could either sponser or participate in workshops that promote information sharing between stakeholders, to bring the best scientific opinions to bear on appropriate animal surrogates, expanding upon previous efforts[9,10]. This would allow stakeholders to "play a major role in both developing … [animal] models and helping define appropriate and efficient pathways for their use in product development," a stated goal in the FDA's Critical Path Initiative[11].

The information provided by a collaboration and such workshops would empower the FDA to develop regulatory guidance or 'points to consider' about specific animal models. Currently, guidance exists for vaccinia virus animal models[12], but not for other diseases in the CDC's Category A list of bioterror pathogens[13]. Even without discussing specifics of individual products, scientists would benefit from open discussion about a number of technical issues, including the appropriate species of animal to model a disease; timelines for moving experimentation into Good Laboratory Practices, which is often expensive and causes delays in development; and developing an animal model to distinguish postexposure prophylaxis from therapy. For example, in humans, a therapeutic would be given after symptoms appear, but in animals, the first clinical indication of active anthrax disease is often sudden death, which makes testing therapeutics difficult. Discussion of relatively well-characterized animal models would benefit from further refinement through information sharing. Even in well-established procedures, sometimes control animals do not die, but recover from a 'lethal' dose of pathogen, making it difficult to assess the efficacy of the therapeutic. Increased sharing of technical information, to the maximum extent possible, can help scientists build increased efficiency into the process, which according to the FDA "is critical both for proper stewardship of what are often limited or ethically sensitive animal resources, as well as for ensuring reliable threat preparedness in a timely manner[11]."

There is precedence for collaborations involving the FDA, industry and academic stakeholders to advance development of medical countermeasures; the Project on Cancer Drug Approval Endpoints sponsors public workshops of scientists from the FDA, industry and academia as well as patient representatives. These workshops address the challenges of developing therapeutics for specific cancers, as 'cancer' covers a wide range of diseases that have different causes and mechanisms, as well as different treatment options. Ultimately, scientific consensus is generated from the workshops, leading to FDA regulatory guidance[14]. The umbrella of different diseases and needed therapies for cancer is comparable to the diversity of diseases and desired medical countermeasures for bioterrorism agents; a similar workshop structure may be beneficial for implementing the Rule.

Another potential model for FDA collaboration with industry and academia is the Product Quality Research Institute (PQRI)[15]. PQRI is a not-for-profit organization that serves as a forum for academia, industry and regulators to work cooperatively to conduct pharmaceutical product quality research and to support development of public standards and regulatory policy. PQRI's scientific findings can be used by FDA to support, improve or create regulatory guidance for the industry.

It is to the FDA's advantage to develop scientific consensus on appropriate animal models for biodefense countermeasures. When products are evaluated for FDA approval, they should be compared on the same yardstick. The current fragmented system leaves companies to develop their own approaches to animal models, which may not be comparable, and which result in an inefficient use of resources.

Recommendation 3

The FDA should develop a consistent interpretation of the Animal Efficacy Rule within the agency. Medical countermeasures for bioterrorism are handled by the same offices as other products applying for FDA approval; for example, the FDA's Center for Biologics Evaluation and Review reviews vaccine candidates and the Center for Drug Evaluation and Review reviews therapeutics. Within these Centers, different offices wrestle with the complexities of the Rule, which may lead to different interpretations and considerations. Although application of the Rule may be different for vaccines and therapeutics, processes should be put into place for greater interdivision and interagency sharing of knowledge of the application of the Rule as appropriate, so review and oversight of biodefense countermeasures are consistent.

Animal efficacy data will never be as convincing as the human efficacy data used for other drugs or vaccines and thus require a different mind-set and consistent strategy to approve countermeasures that are needed in a biodefense emergency. A process that brings disparate parts of the FDA together to share experiences could allow expertise in the Rule to build, allow precedents to be set and guidance to be offered on a variety of countermeasure development steps, including animal models, study designs, labeling and dose-scaling issues, and human safety trial sizes. Guidance early in the process may allow companies to plan for the resources they need to bring a product to licensure.

The path forward

We provide above recommendations for how the Rule can be fine-tuned to improve the development, licensure and stockpiling of biodefense medical countermeasures. It is important that the process for developing medical countermeasures is streamlined so that we can, in the words of HHS Secretary Leavitt, "be better prepared today than we were yesterday…to make America a healthier and safer place"[16]. In the future, implementing the Rule may be even more difficult than it is now: there will be some diseases and therapies that are not possible to model in animals. Achieving the end goal of developing and stockpiling medical countermeasures may eventually necessitate alternative approaches to testing efficacy of human medicines.

The United States faces unprecedented risks to national security in the 21st century posed by the clear and growing danger of bioterrorism and infectious disease epidemics. The Alliance for Biosecurity, in providing these recommendations, seeks to engage the government in a public-private partnership to usher in a new era in the prevention and treatment of severe infectious diseases that present global security challenges. This new era should be characterized by the capacity to rapidly develop, produce and stockpile medical countermeasures to improve the health and security of the country.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

ACKNOWLEDGMENTS
The authors acknowledge the support and legal counsel of Anita Cicero and the Pharmaceutical Practice Group of Drinker Biddle & Reath LLP, for managing the affairs of the Alliance for Biosecurity.

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Conserving biodiversity using patent law

To the editor:

Humans draw immense benefits from using products and derivatives of microbes, plants and animals. And yet, the very foundation of this continuing exploitation, biodiversity, is at risk. Species and natural ecosystems are predicted to disappear in the near future at a faster rate than any time in the history of the Earth. Conservation commands far inadequate resources to halt (or slow down) this process. Here, we suggest a new approach to boost the global resources available for conservation.

Organisms and their genes provide vast resources for humankind that include domesticated plants and animals, medicine, fuel, building materials and ecosystem services[1,2]. For instance, the venom of tropical cone snails *Conus spp.* may contain the largest and clinically most important pharmacopoeia of any genus[3]. Each species of the ~700 known species of cone snails produces 100–200 distinct toxins, so that there may be as many as 140,000 small, highly structured venom peptides, colloquially known as conotoxins[4]. To date only 100 conotoxins have been studied with 77% of ~2,600 research papers focused on one compound, the ω-conotoxin[3,4]. Conotoxins hold much promise for providing a nonaddictive pain reliever 1,000 times more powerful than morphine, and they show prospects for being potent pharmaceuticals in treating neuropathic pain, Alzheimer's disease, Parkinson's disease, epilepsy and clinical depression[3,5]. Of the first 30 peptides purified from *Conus* venoms, 10% reached at least phase 1 human clinical trials[4]. Analgesic *Conus* venom peptides have been attractive development candidates for drugs against severe pain at pharmaceutical and biotech companies because 26 million patients worldwide suffer from some form of neuropathic pain. The global market for neuropathic pain drugs alone is $2.5 billion and this value is expected to double by 2010 (ref. 6).

Cone snails, however, and most of their coral reef habitats are endangered: four species are classified as 'globally vulnerable' by the World Conservation Union (International Union for the Conservation of Nature and Natural Resources, Gland, Switzerland), and more than half the ranges of 69% of cone snail species are directly threatened by humans[3,7]. The resources devoted to preserve cone snail habitats is minuscule in comparison with the expected profits of conotoxin-derivative drugs; for instance, the Asian Development Bank (Manila, Philippines) funded a coral reef rehabilitation project in Indonesia, and the International Coral Reef Conservation Grant pledged $1.2 million for projects mostly in South Asia and the Caribbean[8]. A conservative assumption is that 1% of conotoxins will produce marketable drugs (1,400 drugs) and if each drug may take 1% of market share ($25 million/year), the estimated global market value of conotoxin-derivative drugs is ~$35 billion per year. Assuming that the grant by the Asian Development Bank ($41.3 million/15 years) and Coral Reef Conservation Grant ($1.2 million/year) represent 10% of global funds devoted to coral reef conservation relevant to cone snails, thus the total investment into cone snail conservation is ~$40 million/year, the equivalent of 0.1% market value of conotoxin-derivative drugs is invested back into conserving the source populations in nature. This meager market value versus investment ratio is reminiscent of early colonialists buying Manhattan Island from Native Americans purportedly for $24 worth of merchandise[9].

We suggest that using natural products without acknowledging the contribution by nature should infringe intellectual property rights. Developed societies established tight regulations to acknowledge the process of innovation and protect the rights of innovator. We argue that this concept should be extended to products and genes of organisms from the natural world. Microbes, plants and animals are produced by evolution by natural selection, and this process has lead to a magnificent diversity of species, communities and ecosystems. Converting natural products into marketable drugs by humans only represents the last step following eons of preceding steps leading to a useful product for humankind that have already been carried out by nature.

We propose that inventors (individuals, groups of individuals and companies) that seek to patent nature-based products should be treated as partners (that is, 'joint' or 'co-inventors'). Our rationale is that the process of natural selection itself should be acknowledged as an inventor, given that nature often contributes fundamentally to the formation of the definite and permanent idea of a patent, for instance, a pharmaceutical drug or biomimetic product. We argue that all nature-based patents that do not acknowledge evolution by natural selection as 'co-inventor' should be treated as invalid.