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The FDA's Role in the Development of Bioterrorist Countermeasures

By Marcelo Guerra

Abstract: As the agency that approves drug products used to treat bioterrorist diseases, the FDA plays a significant role in the domestic preparation against a bioterrorist attack. The changes that occurred at the agency in response the AIDS and cancer crises of the 1980's have served as a blueprint for the changes made in response to the terrorist threat. These changes, often desirable but sometimes not, push even further the agency's role as a collaborator in drug development. The paper investigates the threat of a biological weapon attack and the changes to the drug approval process that this threat has prompted.

The FDA's Role in the Development of Bioterrorist Countermeasures

The September 11th attacks and the subsequent anthrax scare have made public officials and the American population more fearful of a terrorist attack with weapons of mass destruction. While only 1% of Americans cited terrorism as the nation's number 1 problem just prior to the attacks, that number spiked to 46% in October of 2001.¹ More recent Gallup Poll survey shows that 82% of Americans see international terrorism as a critical threat, while 75% make the same judgment about the spread of weapons of mass destruction.² Currently, 85% of Americans view terrorism as an important issue on election day, a close second to the state of the economy (86%).³

The increased fear of a terrorist attack has translated into greater government investment in anti-terrorism policies. After the Oklahoma City Bombing in 1995, President Clinton issued Presidential Decision Directive (PDD) 39, a federal plan to respond to similar emergencies or disasters.⁴ Later annexes and directives dealt specifically with federal response to terrorist attacks.⁵ In a 1999 speech to the National Academy of Sciences, President Clinton summarized his administration's efforts to combat the terrorist threat, noting a \$10 billion appropriation to combat terrorism, including \$1.4 billion to protect against biological terror.⁶ This reflected

¹Jeffrey M. Jones, *Sept. 11 Effects, Though Largely Faded, Persist*, THE GALLUP ORGANIZATION, September, 9 2003. The attacks also had significant immediate effects on public expression of patriotism and trust in government. Though these effects dissipated one year after the attacks, less intense but longer term effects remain.

²David W. Moore, *Spread of Weapons of Mass Destruction Most Critical Threats*, THE GALLUP ORGANIZATION, March 8, 2004.

³Frank Newport, *The Potential Impact of Iraq on the Election*, THE GALLUP ORGANIZATION, March 19, 2004. Other surveys have studied the correlation between perceived level of risk and anti-terrorism policy. Surveys conducted two years after the attack show that a significant number of respondents (50%) demonstrate hind-sight bias: reporting that their risk assessments did not rise after September 11th. Respondents who exhibit hind-sight bias are much less supportive of anti-terrorism policies such as passenger screening and surveillance. Nevertheless, all respondents generally support passenger profiling and surveillance policies, particularly those who updated their risk assessments after the attacks. See W. Kip Viscusi & Richard Zeckhauser, *Hind-Sight Choice Bias in Combating Terrorism*, Discussion Paper No. 458 (2004), available at http://www.law.harvard.edu/programs/olin_center/.

⁴See Presidential Decision Directive (PDD) 39, available at <http://www.fas.org/irp/offdocs/pdd39.htm>.

⁵A 1997 Annex by the Federal Emergency Management Agency (FEMA) updated PDD-39 to deal specifically with terrorist threats. In 1998, another decision directive, PDD-62, described various federal agency roles in preparing for and responding to weapons of mass destruction. See PDD-62, available at <http://www.fas.org/irp/offdocs/pdd62.htm>.

⁶William Clinton, "On Keeping America Secure for the 21st Century," remarks before the National Academy of Sciences, Washington, D.C. (January 22, 1999), at <http://cns.miis.edu/research/cbw/nas.htm>.

a 4.3 billion dollar increase in spending since 1997.⁷ By the end of his administration, national preparedness was seen as a top administration priority.⁸

Congress also sought to increase national preparedness for a terrorist attack by passing bills such as the Defense Against Weapons of Mass Destruction Act. The Act provided local law enforcement and first responder units with federal training on how to detect, neutralize, and contain weapons of mass destruction.

⁹ It also required the Department of Defense to designate an official in charge of coordinating federal assistance to local officials, created a rapid response team at the Department of Defense capable of detecting and neutralizing weapons of mass destruction, and provided for training exercises beginning in 1997.¹⁰

Although spending levels on anti-terrorism policies had risen even prior to September 11th,¹¹ that event accelerated the implementation of national security programs and increased spending on domestic preparedness. Following the attacks the Bush administration implemented five new strategies and updated two additional strategies dealing with national security issues.¹² It also established the Department of Homeland Security to coordinate and implement domestic security policies. The 2004 Federal Budget includes \$41 billion in homeland security spending, doubling the funding in 2002.¹³

One area of particular concern is the domestic preparation for a bioterrorist attack. Despite increased spending and programs aimed generally at the terrorist threat, early efforts to prepare for biochemical attacks were limited and often ad hoc.¹⁴ The efforts were often retarded by questions regarding the significance of

⁷GENERAL ACCOUNTING OFFICE (GAO), GAO/T-NSIAD/GDD-99-107, COMBATING TERRORISM: OBSERVATIONS ON FEDERAL SPENDING TO COMBAT TERRORISM 3 (March 11, 1999).

⁸See, e.g., Laurie Garrett, *Plan to Fight New Terrorism*, NEWSDAY, Jan. 23, 1999, at A4; James Benet, *Clinton Tells of Antiterrorism Plans*, N.Y. TIMES, May 23, 1998, at A12.

⁹Defense Against Weapons of Mass Destruction Act of 1996, Pub. L. No. 104-201, §§ 1412(a)(1) & (e)(1), 110 Stat. 2422 (1996).

¹⁰See *id.* §§1413-15.

¹¹See GAO, GAO-02-141T, BIOTERRORISM: PUBLIC HEALTH AND MEDICAL PREPAREDNESS (October 9, 2001) (hereinafter GAO-02-141T).

¹²See GAO, GAO-04-408T, COMBATING TERRORISM: EVALUATION OF SELECTED CHARACTERISTICS IN NATIONAL STRATEGIES RELATED TO TERRORISM, 3 (February 3, 2004) (hereinafter GAO-04-408T).

¹³Office of Management and Budget (OMB), *Winning the War on Terrorism*, at <http://www.whitehouse.gov/omb/budget/fy2004/budget.html>.

¹⁴See GOV. JAMES S. GILMORE, CHAIRMAN, SECOND ANNUAL REPORT TO THE PRESIDENT AND CONGRESS OF THE ADVISORY PANEL TO ASSES DOMESTIC RESPONSE CAPABILITIES FOR TERRORISM INVOLVING WEAPONS OF MASS

biochemical threat.¹⁵ Some members of Congress also questioned whether proposed security measures would inhibit scientific research.¹⁶ As a result, analyses of national preparedness repeatedly emphasized the need to increase efforts in all areas.¹⁷

Emphasizing the need for preparation against this threat, recent legislative and executive efforts have focused on the need to develop countermeasures against potential bioterrorist diseases. Bioterrorist countermeasures, referred to in some legislation as “priority countermeasures,” are drugs, biological products, devices, vaccines, antivirals, or diagnostic tests that may be used to treat, identify, or prevent infection by a biologic agent or toxin that may cause a public health emergency. While many countermeasures for bioterrorist diseases already exist, others will require significant time, effort, and money to research, develop, and produce.

To fill this void, 12 bills were introduced in Congress dealing with the development of countermeasures against a bioterrorism attack,¹⁸ one of which was enacted. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PHSBPRA) has tightened controls on biological agents and toxins and has required the Secretary of Health and Human Services to conduct and award grants to develop countermeasures. In his January 2004 State of the Union address, President Bush proposed further legislation to encourage the development of countermeasures against biological and chemical weapons.¹⁹ Dubbed Project Bioshield, the bill will provide the federal government with additional resources and authority to invest in

DESTRUCTION: II. TOWARD A NATIONAL STRATEGY FOR COMBATING TERRORISM (December 15, 2000) available at <http://www.rand.org/nsrd/terrpanel/terror2.pdf>.

¹⁵See e.g., Daniel S. Greenberg, *The Bioterrorism Panic*, J. COM., Mar. 23, 1999, at 5A; Anthony Shadid, *Funding on Rise for Research into Bioterrorism*, BOSTON GLOBE, Aug. 29, 2001, at A1 (noting that critics have questioned such a substantial investment in a public health threat that... remains, by most accounts, highly unlikely...); Neil C. Livingstone, *Clinton Anti-Terror Plan is Correct*, NEWSDAY, Feb. 3, 1999, at A37 (noting that the Administration’s proposals have been criticized as unnecessary and too costly, designed to frighten the public and usurp traditional civilian authority.).

¹⁶See Aaron Zitner, *Clinton’s 1999 Proposal That Labs Be Required to List All Their Dangerous Agents Failed to Win Congress’ OK*, L.A. TIMES, Oct. 18, 2001, at A13.

¹⁷See *id.*; L. PAUL BREMER III, CHAIRMAN, COUNTERING THE CHANGING THREAT OF INTERNATIONAL TERRORISM: REPORT OF THE NATIONAL COMMISSION ON TERRORISM, (June 5, 2000), available at <http://w3.access.gpo.gov/nct/>.

¹⁸Office of Legislative Policy and Analysis, *Legislative Updates*, (April 18, 2004), at <http://olpa.od.nih.gov/legislation/107/pendinglegislation/6bioterrorism.asp>.

¹⁹Office of the Press Secretary, *President Details Project Bioshield*, (February 3, 2003), at <http://www.whitehouse.gov/news/releases/2003/02/20030203.html>.

and purchase biochemical countermeasures. Current estimates expect \$6 billion in spending over the next ten years.

As the agency that ensures the safety and efficacy of these new products, the FDA plays an important role in the development of bioterrorist countermeasures. The approval process for a new drug involves a tradeoff between ensuring the safety and efficacy of marketed drugs and promoting the availability of new drugs. In the early part of last century, the FDA emphasized the former at the expense of the latter. The emergence of the AIDS crises in the 1980s prompted several changes in FDA policy. The Agency became more willing to accept greater risks in exchange for earlier access and approval of drugs and, more fundamentally, re-envisioned itself as collaborator in the development of new drugs. The emerging bioterrorist threat has pushed this role further: the greater level of risk associated with earlier drug approval is no longer a response to the current need of patients suffering with diseases but to the risk of an outbreak of a bioterrorist disease. This paper will discuss the bioterrorist threat and associated changes at the FDA, analyzing the desirability of change in specific situations, and noting how these changes affect the FDA's role in the drug development process.

A. The Risk of a Biochemical Attack

Separating rhetoric from fact is a crucial first step in determining the changes needed to deal with the threat of a biological attack. The dimensions of the risk involve several factors, including the type of biological agents available, the numbers and type of organizations involved, the motivations to use those agents in an attack, the likelihood of success, and the potential effects of those agents. While some politicians and lawmakers have used hyper-inflated rhetoric in support of anti-terrorism legislation, many experts believe

that large-scale biochemical attacks are improbable in the near future.²⁰ These experts claim that, “in recent years, United States policy to combat the threat of terrorist use of weapons of mass destruction has been driven by perceptions of vulnerability to such attacks rather than the likelihood.”

Although some policymakers emphasize the potentially devastating consequences of an attack, current technical and motivational barriers makes such attacks unlikely in the near future. Conventional weapons and possible small-scale biochemical attacks will remain the most likely short-term risk. However, as technology evolves and terrorist motivations change, large scale biological attacks with potentially dire consequences will become increasingly likely in the future.²¹ Because new drugs often taken several years to develop and approve, this increasing threat requires current attention.

1. High Risk Agents

Domestic vulnerability to a biological attack depends in part on the agents available for an attack and the current treatments for the diseases caused by those agents. Both government and non-government experts have compiled lists of biological agents that may be used in a terrorist attack. Rather than determine which agents are likely to be used (a very uncertain task), the Centers for Disease Control (CDC) has categorized agents primarily based on the agent’s ability to inflict devastating consequences. Other factors include the agent’s environmental resistance, ability to spread from person to person, the size of the effective dose, and the availability of treatment. The list of category A agents – agents that pose a serious threat to national

²⁰“A domestic bioterrorist attack is considered to be a low-probability event, in part because of the various difficulties involved in successfully delivering biological agents to achieve large-scale casualties.” GAO-02-141T, *supra* note 11, at 3. Other reports note that experts have disagreed on the likelihood of biochemical attacks but seem to conclude that the probability is low. GAO, GAO-01-915, BIOTERRORISM: FEDERAL RESEARCH AND PREPAREDNESS ACTIVITIES 1 & 5 (September 2001).

²¹See Margaret Hamburg, *Bioterrorism: A Challenge to Public Health and Medicine*, in PUBLIC HEALTH ISSUES IN DISASTER PREPAREDNESS 93 (Aspen Publications 2001) (“Conventional attacks such as bombs remain the most likely mode of terrorism, but there are many reasons to believe that biological agents may be an increasingly attractive approach.”); JENNIFER BROWER & PETER CHALK, THE GLOBAL THREAT OF NEW AND REEMERGING INFECTIOUS DISEASES 73 n.34 (RAND 2003) (“a large-scale use of [bioweapons] by terrorists is unlikely in the near future because of lack of both motive and technical capabilities.”); Jessica Stern, *Taking the Terror Out of Bioterrorism*, NEW YORK TIMES, April 8, 1998.

health and security – currently includes anthrax, botulism, plague, smallpox, tularemia, and viral hemorrhagic fever.²² Fortunately, the number of agents robust enough to be deployed over a large area is small and in many cases, treatment is currently available.²³

Anthrax is a disease caused by a spore forming bacterium called *bacillus anthracis*, which is found naturally in the soil where it can live for several years. The disease may be contracted through skin (cutaneous) contact, ingestion, and inhalation. The majority of anthrax cases in humans have occurred through cutaneous contact with infected animals. This form of the disease occurs commonly in Asia and sub-Saharan Africa, but is very rare in the United States. Antibiotic therapies are very effective in curing cutaneous anthrax, making the disease rarely fatal. Gastrointestinal anthrax following the consumption of infected animals is also possible but very rare. Inhalation anthrax is the most serious form of the disease but also the most uncommon in nature. In the past inhalation anthrax was an occupational hazard of wool and textile workers but was eliminated through immunization.²⁴

Inhaled anthrax is considered by some to be the agent most likely to be used in a bioterrorist attack. Because the spore form of this bacterium can survive long periods without nutrients or moisture, the organism lends itself towards aerosolization. When aerosolized, the organism behaves like a gas and is resistant to environmental degradation. Thus, in the right conditions, the agent could be spread over a large area and cause high rates of fatality.²⁵ Releasing 50kg of the bacterium upwind of a 500,000 person population center could cause 95,000 deaths and 125,000 hospitalizations.²⁶ On the other hand, anthrax is rarely contagious from person to person, nor do anthrax spores from clothes or skin re-enter the air. Hence the number of

²²Centers for Disease Control and Prevention (CDC), *Emergency Preparedness & Response: Bioterrorism Agents/Diseases Category A*, at <http://www.bt.cdc.gov/agent/agentlist-category.asp> (hereinafter CDC Category A Diseases).

²³Theodore J. Cieslak and Edward M. Eitzen, Jr., *Bioterrorism: Agents of Concern*, in PUBLIC HEALTH ISSUES IN DISASTER PREPAREDNESS 78 (2001).

²⁴See *id.* at 79; CDC Category A Diseases, *supra* note 22.

²⁵Cieslak & Eitzen, *supra* note 23, at 80.

²⁶CDC, *Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices*, 49(1) MORBIDITY AND MORTALITY WKLY. REP. 2 (December 2000) (quoting a World Health Organization estimate).

cases will be limited to those who directly inhale the spores.

When inhaled, anthrax typically has a one to six day incubation period. After incubation, a victim often suffers a flu-like illness, sometimes followed by a period of improvement. Death results in 95 percent of inhalation anthrax cases when not treated within 48 hours after symptoms begin. Currently there are three types of countermeasures against anthrax: vaccinations, antibiotics, and anti-toxin treatments. Although no controlled trials in humans have been performed to validate treatment procedures, limited clinical experience, animal, and *in vitro* tests suggest that cyproflaxin and doxycycline can be used to treat the disease.

²⁷ In addition, some experts recommend both post-exposure vaccination and antibiotic therapy.²⁸

Botulism is a neuroparalytic illness caused by a powerful neurotoxin produced by *Clostridium botulinum*, an anaerobic spore forming bacteria. The disease is transmitted in one of three ways. Infant botulism occurs in a small number of infants who carry *C. botulinum* in their intestinal tracts. Wound botulism occurs when a wound is infected with the bacterium. Food botulism occurs when a person ingests pre-formed toxin, most frequently from home-canned food prepared unsafely.²⁹ Like anthrax, botulism does not spread from person to person nor can it be spread through the air.

A latency period of between one to several days follows exposure. Symptoms usually involve nerve paralysis always beginning with the cranial nerves. If untreated the illness may cause paralysis in the respiratory system, resulting in death. There are 169 yearly US cases, about 5% of which die.³⁰ Although a solitary case may be difficult to diagnose properly, a cluster of symptoms among several patients should make detection easy.

The extensive and prolonged treatment in cases of botulism makes it an attractive agent for a bioterrorist

²⁷CDC, *Update: Investigation of Bioterrorism-Related Anthrax and Interim Guidelines for Exposure Management and Antimicrobial Therapy*, 50(42) MORBIDITY AND MORTALITY WKLY. REP. 2 (October 2001), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm#tab1>.

²⁸Cieslak & Eitzen, *supra* note 23, at 81.

²⁹See CDC, *Disease Information: Botulism*, at <http://www.cdc.gov/ncidod/dbmd/diseaseinfo/botulism.t.htm>; Cieslak & Eitzen, *supra* note 23, at 83.

³⁰See CDC, *supra* note 29.

attack. Patients must receive supportive care and often remain on ventilators for months. A wide scale botulism outbreak would likely strain current medical resources, but the CDC currently has botulism antitoxin that may prevent progression of the disease.³¹

Plague is a now uncommon disease caused by *Yersinia pestis*. Bubonic plague, which is transmitted from the bite of infected rat flea, is the most common naturally occurring form of the disease, with between 1000 and 3000 yearly cases. Because the organism is highly infective, the disease often spreads to other parts of the body. When it infects the bloodstream, the disease is known as septicemic plague. Pneumonic plague, which occurs when the lungs are infected, may also develop from bubonic plague or by inhaling *Y. pestis* from the air.³²

Pneumonic plague is a serious terrorist threat both because *Y. pestis* can be aerosolized and because the disease can spread from person to person. These factors create the possibility that the disease can be spread quickly and widely. In a worst case scenario, the release of 50kg of *Y. pestis* in aerosol form over a city with 5 million inhabitants would cause 150,000 cases of plague, about half of which would require hospitalization.

³³ Bubonic plague may also be a terrorist threat. In fact, Japanese military scientists during WWII used plague-infected fleas to spread bubonic plagues in some areas of China.³⁴

Persons usually become ill two to six days following infection. Symptoms of the disease differ depending on the mode of infection, but fever and malaise are typical. The disease may be treated with prophylactic antibacterial therapy involving streptomycin or gentamicin. Therapy usually must begin 24 hours after the onset of symptoms to be effective. About 14% of cases of plague are fatal, though 100% of pneumonic plague cases are fatal if left untreated.

³¹ See Cieslak & Eitzen, *supra* note 23, at 83.

³² See CDC, *Disease Information: Plague*, at <http://www.bt.cdc.gov/agent/plague/index.asp>.

³³ Ctr. for Biosecurity, *Plague Fact Sheet*, at http://www.upmc-biosecurity.org/pages/agents/plague_facts.html.

³⁴ Curtis D. Malloy, *A History of Biological and Chemical Warfare and Terrorism*, in PUBLIC HEALTH ISSUES IN DISASTER PREPAREDNESS 87 (2001).

Outbreaks of smallpox have occurred continually for thousands of years, but the disease was eliminated through a successful worldwide vaccination campaign. The last reported case of naturally occurring smallpox was treated in Somalia in 1977. The disease is caused by a variola virus spread from person to person through face to face contact (particularly when the infected person is coughing), contact with infected body fluids, or contact with infected objects such as bedsheets. Though rare, the disease sometimes can spread through the air.³⁵

Typically there is a 12 to 14 day incubation period following exposure. The first symptoms include fever, malaise, aches, and vomiting. After a period of about three days, a rash emerges as red dots in the tongue and mouth. The dots develop into sores which break open. Soon afterwards, a rash develops on the skin spreading downwards from the face to all parts of the body. In a period usually lasting 12 days, the rash develops into bumps, then pustules, then scabs. Eventually the scabs fall off, leaving scars. Once the scabs have fallen off, the person is no longer contagious. Death occurs in about 30 percent of cases.

Several factors make smallpox an attractive agent to terrorists. Most persons no longer are vaccinated against the virus, and vaccine stockpiles are dwindling. Moreover, there is no effective treatment for the disease, though vaccination within the first few days after exposure may prevent the disease from occurring. Currently only two maximum security facilities maintain stockpiles of the virus, making acquisition of the virus difficult. However, other unknown stockpiles may exist, and reconstruction of the virus may soon be possible since its entire genomic sequence is known.

Tularemia is an illness caused by *Francisella tularensis*, a bacterium often found in animals. The disease can spread in several ways: being bitten by infected fleas or other insects, handling infected animals, or

³⁵CDC, *Emergency Preparedness & Response: Smallpox*, at <http://www.bt.cdc.gov/agent/smallpox/index.asp>.

breathing in the bacterium. Typically the disease does not spread from person to person.

Several non-specific flu-like symptoms are associated with tularemia, making detection difficult. Symptoms usually start three to five days after exposure. If left untreated, the disease can be fatal. However, several antibiotics may be used to treat the disease, and the FDA is currently reviewing a vaccination against the disease.

The highly infectious nature and natural abundance of *F. tularensis* makes it an attractive bioterrorist agent. Breathing even a few bacteria could cause fatal pneumonia. However, manufacturing an aerosol version of the bacterium is a technically sophisticated task.³⁶

Viral hemorrhagic fevers are a group of diseases caused by four types of RNA viruses. While the diseases differ in symptoms, severity, and mode of transmission, they typically damage the vascular system and the ability of the body to regulate itself. The virus typically lives in infected animal hosts. Humans typically acquire the virus by coming into contact with the host. The viruses may also be infectious via aerosol or from person to person (as is the case with Ebola virus), causing them to be a high priority concern. While patients may receive supportive therapy for their disease, there is no established cure. Vaccines have developed for yellow fever and Argentine hemorrhagic fever.

2. The Motivation to Use a Biological Agent

The past use of biological weapons has been isolated to a few, amateurish or low-consequence events. For example, in 1984, members of an Oregon cult plead guilty to pouring culture of *Salmonella Typhimurium* in salad bars and coffee creamer containers in an effort to influence an upcoming election.³⁷ 751 people became

³⁶CDC, *Emergency Preparedness & Response: Tularemia*, at <http://www.bt.cdc.gov/agent/tularemia/index.asp>.

³⁷See Malloy, *supra* note 34, at 90.

ill. A comparable event occurred in Wakayama, Japan, where a person intent on committing insurance fraud poisoned curry with arsenic. Sixty-seven people became ill. Finally, the anthrax letter attacks created a great deal of fear and cost the U.S. Postal Service \$5 billion, but they ultimately caused only five deaths and seventeen infections.³⁸ While historical precedent for biological attacks is limited, the lack of precedent does not equate with the absence of a threat. Attacks with biological agents have become more frequent due to the emergence of new kinds of terrorist organizations. In the near future, these organizations will continue to launch small-scale attacks, but large-scale attacks will become more likely as terrorist organizations update capabilities.

The emergence of a new kind of terrorist organization increases the likelihood of future biological attacks. Despite public belief that terrorists are irrational, traditional terrorist organizations do not wish to cause mass, indiscriminate casualties, seeing such attacks as unnecessary, counterproductive, or immoral.³⁹ For instance, the E.T.A., a Basque separatist organization, usually attacks symbolic targets and makes warning calls before their attacks.⁴⁰ Both they and the I.R.A. have previously issued apologies for killing innocent civilians.⁴¹ These organizations are well aware that mass casualty produced by biological weapons may cause a backlash among their supporters.

While most terrorist organizations continue to shy away from mass-casualty attacks, some terrorist organizations have demonstrated both their desire and ability to carry out such attacks. These organizations share several characteristics that increase the likelihood that they will use biological weapons: less apparent

³⁸See BROWER & CHALK, *supra* note 21, at 73.

³⁹See *Hearings before the House Subcommittee on National Security of the Committee on Government Reform*, July 26, 2000 (statements of W. Seth Carus); Joseph F. Pilat, "Bioterrorism: Homeland Defense: Next Steps," Presentation at RAND symposium, Santa Monica, CA (February 8-10, 2000).

⁴⁰*Spain Maintains ETA Is Main Bomb Suspect a Day Before Elections*, BLOOMBERG NEWS, March 13, 2004, available at http://quote.bloomberg.com/apps/news?pid=10000087&sid=atgcW6VC7eKA&refer=top_world_news.

⁴¹See JEFFREY D. SIMON, *TERRORIST AND THE POTENTIAL USE OF BIOLOGICAL WEAPONS: A DISCUSSION OF POSSIBILITIES* 5 (RAND, 1989).

ideological or political commitments, charismatic leadership, no well-defined outside constituency, and a sense of paranoia or grandiosity.⁴² Within this group, religious fundamentalists pose the greatest threat.⁴³ As one expert explains, “if a terrorist believes that acts of violence are not only politically but also morally justified, he has a powerful incentive for any type of terrorist attack.”⁴⁴

Several factors make biological weapons an attractive choice for these organization. First, some biological agents are relatively easy to come by: several already exist in nature while others could be bought or stolen from legitimate facilities.⁴⁵ Second, biological weapons may be difficult to detect, making it more likely that terrorists will get away with an attack. Third, the release of a biological agent generates fear,⁴⁶ and that which instills fear also captures headlines, bringing attention to a terrorist’s ideology or mission:

With terrorist attacks occurring on an almost daily basis, the public and the media have become somewhat desensitized. And with a multitude of terrorist groups ‘competing’ for the international spotlight, more dramatic incidents are likely in the future.

Finally, biological weapons could cause a great deal of harm. Although bioterrorist attacks have not claimed many lives to date, estimates of worst-case scenarios are daunting.⁴⁷ The WHO has estimated that 36 thousand people could die if 50 kilograms of *Y. Pestis* were released as an aerosol in a city of five million. Some Congressional estimates of an aerosolized anthrax attack on Washington, D.C. place the death toll at between 130,000 to three million.⁴⁸ Under the right conditions, a large-scale biological attack could kill hundreds or even thousands of people.

⁴² See id.; Jonathan B. Tucker, *Historical Trends Related to Bioterrorism: An Empirical Analysis*, 5(4) EMERGING INFECTIOUS DISEASES (July-August 1999), at <http://www.cdc.gov/ncidod/EID/vol5no4/tucker.htm>.

⁴³ Pilat, *supra* note 39.

⁴⁴ SIMON, *supra* note 41, at 7.

⁴⁵ See Cieslak & Eitzen, *supra* note 23, at 78.

⁴⁶ The potential of a biological attack to instill fear in a population is evident from the anthrax scare or from the several hoaxes that have occurred in the past few years. See Leonard A. Cole, *Bioterrorism Threats: Learning from Inappropriate Responses*, in PUBLIC HEALTH ISSUES IN DISASTER PREPAREDNESS 66 (2001), (listing 40 selected anthrax hoaxes between 1997 and 1999 and discussing the responses to each).

⁴⁷ *Id.*

⁴⁸ See Ctr. for Biosecurity, *Anthrax Fact Sheet, 1999*, at http://www.upmc-biosecurity.org/pages/agents/anthrax_facts.html.

An attack could also have a significant impact on the economy even if it failed to claim any lives. Direct expenses would include money spent on clean food and water, medicine, equipment, and medical personnel, as well as costs incurred from setting up effective quarantines. Some estimates of the anthrax scare following September 11th suggest that state health departments spent more than a quarter billion dollars responding to these attacks.⁴⁹ Though difficult to estimate, indirect costs like lost productivity and decreased faith in the financial markets could also be significant. A U.S. ban on Chilean grapes following the discovery of two cyanide-tainted grapes significantly harmed the Chilean economy, and the World Trade Center attacks caused millions in losses.⁵⁰

In light of this significant economic effect, some previous biological attacks were aimed not at creating casualties but at disrupting markets. For instance, in 1978 Palestinian extremists injected mercury into Israeli oranges with the stated goal of damaging the Israeli economy.⁵¹ Bin Laden and other members of Al-Qaeda have also threatened to attack economic targets to destabilize the American economy.⁵² The potential economic effects are great from both perceived and real threats.

Finally, a large-scale attack would have a substantial psychological impact that could threaten the ability of governments to function and leave the nation in disarray. The Federal government has conducted several simulation exercises to estimate the extent of the damage and measure the degree of preparedness. One exercise dubbed “Dark Winter” presented the scenario of a smallpox release in shopping malls in Oklahoma City, Philadelphia, and Atlanta with the initial infection of three thousand people. Within two weeks, 160,000 smallpox cases in twenty-five states were estimated to occur.⁵³ The rapid spread of the disease quickly

⁴⁹147 Cong. Rec. S. 13902 (2001) (statements of Senator Biden).

⁵⁰See *id.* at 11.

⁵¹See SIMON, *supra* note 41, at 9.

⁵²See GOV. JAMES S. GILMORE, CHAIRMAN, FOURTH ANNUAL REPORT TO THE PRESIDENT AND THE CONGRESS OF THE ADVISORY PANEL TO ASSESS DOMESTIC RESPONSE CAPABILITIES FOR TERRORISM INVOLVING WEAPONS OF MASS DESTRUCTION: IMPLEMENTING THE NATIONAL STRATEGY 10 (December 15, 2002) (hereinafter FOURTH ANNUAL GILMORE COMMISSION REPORT) (quoting tapes from Bin Laden and other Al-Qaeda members).

⁵³See Tara O’Toole, Thomas V. Inglesby, Jr., and Michael Mair, *Shining Light on Dark Winter*, 34 CLINICAL INFECTIOUS DISEASES 972 (2002), available at <http://www.journals.uchicago.edu/CID/journal/issues/v34n7/020165/020165.html>.

overwhelmed the health care system and left the nation in chaos.⁵⁴ In another simulation exercised dubbed TOPOFF, the scenario presented was the release of *Y. Pestis* in the Denver Performing Arts Center, leading to 500 symptomatic victims within three days. Four days after the release, officials estimated that between 3700 to 4000 people became infected, leading to 950 and 2000 deaths.⁵⁵

While many terrorists have not insisted upon causing such devastating damage, recent changes to terrorist motivations suggest that attempts at large-scale attacks will become increasingly more likely in the future. Biological agents present terrorists with a good choice for these terrorist organizations to inflict physical, economic, psychological, and political harm on a population. These changes suggest that terrorist organizations may increase their efforts to acquire or develop biological weapons, increasing the threat of future biological attacks.

3. Technical Barriers to a Biological Attack

Although some terrorists possess the right motives and incentives to use biological weapons, terrorists face significant technical barriers in preparing for a large-scale biological weapons attacks. Although some highly infectious biological agents are not hard to find in nature or to acquire from legitimate sources,⁵⁶ many others, like smallpox, are difficult to come by.⁵⁷ Moreover, recognizing and isolating the particularly lethal strains requires a great deal of expertise and technologically sophisticated equipment.⁵⁸ Purifying and

⁵⁴See Nicholas Kristoff, *Lock 'Em Up*, NEW YORK TIMES, May 2, 2003, at A33.

⁵⁵See Thomas V. Inglesby, Rita Grossman, and Tara O'Toole, *A Plague on Your City: Observations on TOPOFF*, 32 CLINICAL INFECTIOUS DISEASES 436 (2001), available at <http://www.journals.uchicago.edu/CID/journal/issues/v32n3/001347/001347.html>.

⁵⁶"*Clostridium botulinum*, for example, is ubiquitous in soil and cultured easily by anyone with modest training in microbiology. Ricin is extracted readily from castor beans. . . recipes for its production are disseminated widely and available on the internet. . . . Clinical laboratories handle cultures of [potential agents] and constitute a potential source for their acquisitions." Cieslak & Eitzen, *supra* note 23, at 80.

⁵⁷See Tara O'Toole, *Smallpox: An Attack Scenario*, 5(4) EMERGING INFECTIOUS DISEASES 540 (July-August 1999) available at <http://www.cdc.gov/ncidod/EID/vol5no4/otoole.htm> ("The international black market trade in weapons of mass destruction is probably the only means of acquiring [smallpox].").

⁵⁸See GOV. JAMES S. GILMORE, CHAIRMAN, FIRST ANNUAL REPORT TO THE PRESIDENT AND THE CONGRESS OF THE ADVISORY PANEL TO ASSESS DOMESTIC RESPONSE CAPABILITIES FOR TERRORISM INVOLVING WEAPONS OF MASS DESTRUCTION: ASSESSING

manufacturing these agents pose even more significant hurdles. *Botulinum toxin*, for instance, often loses its toxicity during purification. And turning *b. anthracis* into a form appropriate for an attack, “necessitates a combination of skill and extreme care during a production technique that involves the application of heat or chemical shock.”⁵⁹ Mass production also requires the use of technically sophisticated equipment that may be difficult to acquire and will increase the risk of detection.⁶⁰ Preparing an agent for deployment also presents a significant technical barrier. Terrorists will likely need to aerosolize an agent to inflict mass casualties on a population. However, only a few agents are suitable for aerosol contamination. Moreover, turning these agents into an aerosol requires expensive equipment, often destroys the organism, and entails significant risk that the terrorist will accidentally infect himself.⁶¹ Effective outdoor deployment also requires the cooperation of meteorological factors (though deployment in a building would avoid this variable).

Previous failures demonstrate the difficulty of acquiring and developing high-impact biological weapons. On eight occasions between 1990 and 1995, Aum Shinrikyo, a Japanese religious cult, attempted to aerosolize anthrax and botulitum toxin to use in attacks on the Japanese subway system. Despite being well organized and funded, the group failed on each occasion to develop the weapon, opting instead to attack with sarin gas.

Given the current capabilities of terrorists organizations, small-scale attacks will continue to be the norm in the near future. As one expert explains,

Crude bioterrorism does not really require advanced technologies or specialized equipment. In any case, the production of biological agents can be undertaken in a small facility, with no readily identifiable distinguishing features or signatures. Few precursor materials are essential, although growth media are needed to produce significant quantities of an agent.⁶²

THE THREAT 21 (December 15, 1999) (hereinafter FIRST ANNUAL GILMORE COMMISSION REPORT). In 2002, the Commission reaffirmed its conclusion that the barriers to developing high-impact biological weapons were formidable. See FOURTH ANNUAL GILMORE COMMISSION REPORT, *supra* note 52, at 18.

⁵⁹FIRST ANNUAL GILMORE COMMISSION REPORT, *supra* note 58, at 21.

⁶⁰See *id.*

⁶¹See *id.*

However, the increasing accumulation and dissemination of know-how may place high-impact biological weapons within the reach of many terrorist organizations. Research activities into biological agents are “dual use,” having the potential to be used both defensively and offensively.⁶³ For instance, scientists interested in controlling rodent populations have created an extremely virulent mousepox to sterilize mice, but the technique was also useful in creating a virulent smallpox weapon.⁶⁴ Thus, “the knowledge that is being accumulated in the basic biochemistry of infection is going to make it a lot easier to perfect biological weapons than to build defenses against them.”⁶⁵

Moreover, several simultaneous events have increased the dissemination of information necessary to develop biological weapons. Technological progress in many parts of the world creates the possibility that legitimate biological facilities may be exploited to produce biological agents or to mask biological weapons agents.⁶⁶ Many countries may not have the resources or concern to invest in significant security for these facilities. More generally, progress in the basic sciences and dissemination of that information may also increase the risk of serious biological attacks.⁶⁷ Finally, the internet may also serve as a new medium for disseminating knowledge, providing easy access to important information.⁶⁸

The potential recruitment of knowledgeable scientists also creates a significant threat that terrorist will increase their capabilities. The poor economic condition and inadequate physical security in the former Soviet Union and other countries creates conditions ripe for the recruitment of scientists and the acquisition of agents. In this environment, scientists with biological or bioweapons experience may sell their expertise

⁶³For a discussion of dual use technologies, see Gigi Kwik, Joe Fitzgerald, Thomas Inglesby, Tara O’Toole, *Biosecurity: Responsible Stewardship of Bioscience in an Age of Catastrophic Terrorism*, 1(1) BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY, PRACTICE, AND SCIENCE 27-35 (2003).

⁶⁴See BROWER & CHALK, *supra* note 21, at 73.

⁶⁵Joshua Lederberg, “Bioterrorism Homeland Defense: Next Steps,” Presentation at RAND Symposium, Santa Monica, CA (February 8-10, 2000).

⁶⁶John M. Lauder, Statement by Special Assistant to the DCI for Nonproliferation John A. Lauder on the Worldwide Biological Warfare Threat to the House Permanent Select Committee on Intelligence (March 3, 1999), at http://www.cia.gov/cia/public_affairs/speeches/1999/lauder_speech_030399.html.

⁶⁷WORLD HEALTH ORGANIZATION (WHO), HEALTH ASPECTS OF BIOLOGICAL AND CHEMICAL WEAPONS 16 (2001) (hereinafter “WHO 2001”).

⁶⁸See FIRST ANNUAL GILMORE COMMISSION REPORT, *supra* note 58, at 49; George J. Tenet, Worldwide Threat 2001: National Security in a Changing World, statement before the Senate Select Committee on Intelligence (February 7, 2001).

to the highest bidder. “By importing talent and buying technology, state and non-state actors can make dramatic leaps forward...including the development of new agents and delivery systems, a much earlier achievement of indigenous capabilities, and more sophisticated denial and deception techniques.”⁶⁹ In fact, some scientists have already been recruited by potentially terrorist states.⁷⁰ Aum Shinrikyo has also actively recruited graduate scientists and technicians.⁷¹

One final note: the discussion above has focused on the threat from individual terrorist organizations. Some claim that the greatest current threat comes not from these terrorist organizations but from state-sponsored terrorists. Some states possess the human and physical capital required to surmount the technical hurdles mentioned above. Moreover, the leadership of these countries may believe in engaging in risky enterprises, or they may support terrorist organizations in their efforts to acquire and develop biological weapons.⁷² Several “hostile” states such as Iran, Libya, North Korea, and Syria have or are developing offensive biological weapons capacities⁷³ despite treaties banning the proliferation of these weapons. Fortunately, the likely political or military repercussions a state will face for their support of biological warfare may dissuade many from using their capacity to further terrorist objectives.

Evaluating the current and future risk of a biological attack is fraught with uncertainty, particularly because much of the evidence is anecdotal or speculative. One cannot discount the possibility that new events or new information will mitigate the risk or the uncertainty of future attacks. This could occur as a result of specific events, like capturing fundamentalists or discovering the extent of a country’s biological weapons program, or more general ones, like passing tougher international treaties against proliferation or increasing

⁶⁹Lauder, *supra* note 66.

⁷⁰See Jonathan B. Tucker and Kathleen M. Vogel, *Preventing the Proliferation of Chemical and Biological Weapons and Know How*, 71 THE NONPROLIFERATION REVIEW 88, 89 (Spring 2000); Lauder, *supra* note 66.

⁷¹See WHO 2001, *supra* note 67, at 83.

⁷²One commentator notes that a biological weapons release by a hostile state would look like a terrorist one, making detection difficult. See Carus, *supra* note 39.

⁷³See *id.*; Lauder, *supra* note 66.

surveillance on the Internet. Despite these possibilities, historical trends demonstrate a rise in the use of biological agents as weapons. Bioterrorism incidents, both actual and hoaxes, increased sharply from about a dozen yearly incidents in the early 1990's to 181 incidents in 1998.⁷⁴ At the same time, the vast majority (87%) of attacks against U.S. interests have involved bombs or conventional explosives.⁷⁵ Because bombs and hijackings require less preparation and investment than biological weapons, many believe that these weapons will continue to pose the most likely current threat.⁷⁶ Nevertheless, with more groups interested in biological weapons and an ever-increasing capability to develop these weapons, the risk of a biological attack will likely continue to rise, with small-scale attacks posing the greatest current biological threat.⁷⁷

B. Developing Bioterrorist Countermeasures

The inherently speculative nature of drug research and development makes it a very costly undertaking. It typically takes 10 years to move a drug from pre-clinical studies to market.⁷⁸ For every drug that does make it, thousands of compounds must be screened in pre-clinical trials.⁷⁹ Moreover, only 20% of the compounds entering clinical trials gain FDA approval.⁸⁰ One controversial study has estimated that the *out of pocket* costs are \$400 million for each new drug.⁸¹ The figure includes money spent on discovery, pre-clinical and

⁷⁴See Tucker, *supra* note 42.

⁷⁵See Laura Parker, *Terrorists Most Likely Weapon Here: Bombs*, USA TODAY, May 16, 2003, at 1A (“many analysts are concerned by what they see as overblown descriptions – by the media and the government – of the threats that unconventional weapons pose, which the analysts say have perpetuated myths about how serious the risks are.”).

⁷⁶See *id.*

⁷⁷See also, *CIA report says Al-Qaida attacks could be small-scale*, CIDRAP News, at <http://www.cidrap.umn.edu/cidrap/content/bt/bioprep/btwatch/btwatch-jun-2003.html> (“Al-Qaida’s ultimate goal is to use chemical, biological, or nuclear weapons to cause mass casualties, but the group and associated extremists are likely to launch small rather than large-scale attacks, according to a CIA report prepared last month.”).

⁷⁸See Henry Grabowski, *Pharmaceuticals: Politics, Policy, and Availability: Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEO. PUBLIC POL’Y REV. 7, 9 (2003) (citing

DiMasi, J.A. 1995a. Success Rates for New Drugs Entering Clinical Testing in the United States. *Clinical Pharmacology and Therapeutics* 58:1-14); see also, CHARLES E. HAMMER, *DRUG DEVELOPMENT* 2 (1982) (“The odds of success in discovering a new drug are very small.”).

⁷⁹See Grabowski, *supra* note 78, at 9 (citing DiMasi 1995).

⁸⁰See *id.*

⁸¹See, Grabowski, *supra* note 78, at 9 (citing DiMasi, J.A., R.W. Hansen and H.G. Grabowski. 2003. The Price of Innovation: New Estimates of Drug Development Costs, *Journal of Health Economics* 22:151-185). Several groups have questioned this figure’s accuracy, noting that it did not account for the tax incentives and government grants given to pharmaceuticals, and that the study’s author received his funding from the pharmaceutical industry. See Ceci Connolly, *Price Tag for a New Drug:*

clinical trials, and an allocation for the cost of failure. Expenditures in the clinical phase account for 70% of these costs, reflecting the high per-patient costs of clinical trials, the number of patients required, and the failure rate of these trials.

In the drug business, time is also money. Long clinical trials and approval times delay the time it takes to recoup R&D investment, increasing the cost of capital. The study above estimates that, because of the long R&D times involved, the capitalized costs for new drugs is \$802 million. This figure nearly tripled the \$231 million estimate released by the authors in 1987.⁸² More recent figures by the same author estimate capitalized costs at \$897 million, a thirty percent increase.⁸³

Drug companies undertake these expenses knowing that hitting a winner means big payoffs. In a sample of 118 compounds studied by DiMasi, about one half of the revenue is accounted for by the top tenth of new drug introductions, and only the top three deciles cover average R&D costs.⁸⁴ Top selling drugs achieve peak sales in the hundreds of millions (or low billions) of dollars, while lower selling drugs account for sales in the tens of millions.⁸⁵ These figures suggest that a few top selling drugs account for the long run economic success of the pharmaceutical industry.

The market for many bioterrorist countermeasures is significantly different than that of new drugs. The broad category of bioterrorist countermeasures includes several different types of products ranging from general use antibiotics to detection and analysis equipment to special vaccines against bioterrorist agents. There are many private and public buyers ready to purchase some of these products either for non-terrorist purposes or

\$802 Million, WASHINGTON POST, December 1, 2001, at A10.

⁸² See Press Release, *The Ballooning Price Tag*, December 4, 2001, at <http://www.tufts.edu/communications/stories/120401BallooningCosts.htm>.

⁸³ *New Drugs Get a Heftier Price Tag*, BOSTON BUSINESS JOURNAL, May 13, 2003, at <http://boston.bizjournals.com/boston/stories/2003/05/12/daily16.html>.

⁸⁴ See, Grabowski, *supra* note 78, at 9.

⁸⁵ See *id.*

in preparation for a biochemical attack. However, other countermeasures do not serve any current purpose and therefore have a small or insignificant market. Facing these conditions, many companies may not be willing to invest the money required to develop these countermeasures while foregoing the blockbuster profits from other drugs.

Given the numerous dimensions of the problem, several agencies have brought their expertise to bear to solve this perceived market failure. In general, the NIH (usually through the National Institutes of Allergies and Infectious Diseases, or NIAID) conducts or supports research to promote the development of countermeasures.⁸⁶ Research efforts include both basic research into virology or immunology and clinical studies, including funding the clinical trials for biological countermeasures. The Department of Health and Human Services (DHHS) purchases countermeasures for use in the case of a biological or chemical attack.

Finally, the Food and Drug Administration (FDA) requires testing to ensure that countermeasures are the safe and effective. In an effort to lower costs and to deal with the problems peculiar to countermeasure development, the FDA has updated several of its requirements for testing the safety and efficacy of these drugs. These changes, desirable in some situations and undesirable in others, pushes the FDA further into the role of drug development collaborator, a change that first occurred in response to the AIDS and Cancer crises of the 1980's.

1. History of FDA Regulation

FDA's regulatory authority over foods, drugs, and cosmetics began in the early part of the last century. Around that time, members of Congress and other groups became concerned with the quality and safety

⁸⁶Research may also be conducted by several other departments, such as the Department of Defense (DoD) or the CDC.

of ‘patent’ medications and nostrums.⁸⁷ Many of these drugs were at best ineffective and at worst seriously unsafe. Manufacturers marketed nostrums to deal with conditions ranging from cancer and epilepsy to baldness and bust-lines.⁸⁸ Many contained nothing but worthless ingredients. For instance, analysis of one medicine, Dr. Kilmer’s Indian Cough Cure, revealed that it contained mostly alcohol, water, and sugar. Other medications, some given to children, contained dangerous ingredients such as morphine.⁸⁹ In this environment, consumer, industry, and medical groups began calling for a bill that would control the sale of these drugs and deal with the problem of food adulteration. Congress worked on several versions of the bill, but it did not pass a final act until after the publication of *The Jungle*, a book detailing the unsanitary conditions of Chicago’s meat packing industry. The controversy surrounding the book finally spurred a final action. Congress passed the Pure Food and Drugs Act in 1906.⁹⁰

Subsequent efforts to enforce the law revealed that it contained several weaknesses. The law prohibited the shipment in interstate commerce of adulterated or misbranded foods or drugs but did not call for any pre-market drug testing and did not require ingredient or warning labels. Instead, the law relied on post-marketing seizure of the offending product and provided for civil and criminal penalties to deter misbranding and adulteration.⁹¹ In each case, the Bureau of Chemistry (the precursor to the FDA) had to petition the courts to stop the distribution of the offending product. As later interpreted by the Supreme Court, the original law also could not prohibit false therapeutic claims.⁹² Subsequent amendments closed this loophole, but the Bureau still had to show that the seller had actual knowledge that the claims were false.⁹³ A defendant could escape conviction simply by proving his subjective belief that his product worked.⁹⁴

⁸⁷ See James Harvey Young, *The Long Struggle for the 1906 Law* (1981), at <http://www.cfsan.fda.gov/~lrd/history2.html>.

⁸⁸ See *The Patent Medicine Menace*, at <http://www.fda.gov/cder/about/history/Gallery/galleryintro.htm>.

⁸⁹ For examples, see 2 ARTHUR J. CRAMP, ED., *NOSTRUMS & QUACKERIES* (1921).

⁹⁰ See Pure Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906).

⁹¹ See *id.*; Wallace F. Jansen, *The Story of the Laws Behind the Labels, Part II*, FDA CONSUMER (1981), at <http://vm.cfsan.fda.gov/~lrd/histor1a.html>.

⁹² See *United States v. Johnson*, 221 U.S. 488 (1911).

⁹³ See Jansen, *supra* note 91.

⁹⁴ See *id.*

Congress has strengthened FDA's power several times over the last century. The first major change occurred in 1938 when Congress enacted the Federal Food, Drug, and Cosmetic Act.⁹⁵ Unlike the 1906 Act, the 1938 Act created a pre-market notification regime whereby manufacturers were required to notify the FDA prior to marketing a new drug.⁹⁶ The FDA was authorized to challenge the product's safety, to request injunctions against the distribution of unsafe products, and to inspect factories. Moreover, a showing of fraud was no longer required to prevent the distribution of products containing false claims.⁹⁷

Like its predecessor, the 1938 Act contained several limitations. In particular, the FDA had the burden of showing that the product was unsafe, and it had no authority to regulate the efficacy of new drugs. Amendments in 1962 made three important changes to further strengthen FDA's control. First, the Amendments created a pre-market approval regime which barred the distribution of a new drug until it obtained clearance from the FDA. Second, the Act directed the FDA to test new drugs for both safety and efficacy, specifying that "substantial evidence" was required to demonstrate effectiveness. Finally, the FDA received expanded authority to control clinical trials and to establish standards under which drugs could be shipped for such trials.⁹⁸ While the law has been amended several times since 1962,⁹⁹ the basic structure has remained the same.

The FDA came to regulate biologics through a different series of historical events. Biologics are products derived from living sources and include products like vaccines, serums, and toxins. These products first came under regulation in 1902, when congress passed the Biologics Control Act in response to the distribution of tetanus-infected diphtheria anti-toxin. The Act intended to prevent the loss of public confidence over the then emerging national vaccination program by making it unlawful to distribute biologics not prepared at

⁹⁵ See Federal Food, Drug, and Cosmetics Act, Pub. L. No. 75-716, 52 Stat. 1040 (1938) (hereinafter FD&C Act).

⁹⁶ See Jansen, *supra* note 91.

⁹⁷ See *id.*

⁹⁸ See Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

⁹⁹ In particular, the FDA was formally authorized to regulate medical devices in 1976. See Medical Device Amendments of 1975, Pub. L. No. 98-21, 90 Stat. 539 (1976). In 1992, FDA was authorized to impose fees on manufacturers to fund activities related to drug approval. See Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992).

licensed establishments.¹⁰⁰ A newly created biologics review board was authorized to test biologic products and to inspect manufacturing establishments.

As was the case with food and drugs, government control over biologics has been ratcheted up gradually throughout this century. The Public Health Services Act of 1944 required that manufacturers demonstrate that their products were “safe, pure, and potent” as a condition of licensing.¹⁰¹ Although the Act did not mention effectiveness, proof of effectiveness was later imposed at the agency level. Authority to regulate biologics bounced from agency to agency until power was transferred to the FDA in 1972. That same year, the FDA issued regulations that brought biologics under the control of the FD&C Act.¹⁰² This action, later codified by legislation,¹⁰³ made the requirements for biologics analogous to those of drugs.

2. The Approval Process for Drugs & Biologics

Drugs and biologics must currently undergo a rigorous approval process before distribution to the public. The FD&C Act prohibits the distribution of any new drug unless the FDA approves an application for the use of that drug.¹⁰⁴ To cross this hurdle, a drug’s safety must be adequately tested by “all methods reasonably applicable.”¹⁰⁵ There must also be “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions prescribed.”¹⁰⁶ The Act defines substantial evidence as,

¹⁰⁰ See Biologics Control Act of 1902, Pub. L. No. 57-243, 32 Stat. 728 (July 1, 1902).

¹⁰¹ See Public Health Service Act, Pub. L. No. 78-410, §351, 58 Stat. 682 (July 1, 1944); 42 U.S.C. § 262(a)(2)(C)(i)(I) (2004).

¹⁰² See 37 Fed. Reg. 4004 (February 25, 1972).

¹⁰³ See 42 U.S.C. § 262(j) (2004).

¹⁰⁴ See 42 U.S.C. § 355(a) (2004).

¹⁰⁵ See 42 U.S.C. § 355(d) (2004).

¹⁰⁶ *Id.*

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.¹⁰⁷

The statute clearly requires, albeit it in broad terms, that a new drug must be adequately tested before distribution. In its regulations and guidance documents, the FDA has clarified the statute by specifying the quantity and types of studies required for approval. Generally, preclinical tests on animals and clinical tests on humans are required to meet the statutory criteria.¹⁰⁸ In keeping with standard scientific practice, clinical trials must be randomized and controlled.¹⁰⁹ Randomized clinical trials require that researchers randomly assign study participants to one of two groups: the study group that receives the drug being tested and the control group that receives a substance other than the drug (such as a placebo). In this way, the researcher can better attribute the observed differences between the test groups to the effects of the treatment alone.¹¹⁰ Before human testing can begin, the drug's sponsor must first obtain an exemption from the Act's prohibitions. Exemption may be obtained from the FDA by filing for a claimed exemption for an investigational new drug (IND).¹¹¹ The IND protects the safety of human subjects by ensuring that the investigational drug has undergone adequate laboratory and animal tests for safety and usefulness. It also ensures that the clinical trials adequately protect the human subjects and are scientifically designed. The FDA takes four factors into account when approving an IND: the protection of the human research subject, the adequacy of animal studies already completed and analyzed, the scientific merits of the research plan, and the qualifications of the investigator.¹¹² FDA regulations also require that an Institutional Review Board (IRB) approve the

¹⁰⁸ See 21 C.F.R. §§ 312.22 & 312.23(a)(8) (2004); FDA, FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS 14-24 (1999), available at <http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf>.

¹⁰⁹ See Jennifer Kulynych, *Will FDA Relinquish the Gold Standard for New Drug Approval? Redefining Substantial Evidence in the FDA Modernization Act of 1997?*, 54 Food & Drug L.J. 127, 131 (1999) (discussing the history and role to the randomized clinical trial in the FDA approval process).

¹¹⁰ See *id.*

¹¹¹ See 21 C.F.R. § 312.20 (2004).

¹¹² See 21 C.F.R. § 312.22(a) (2004).

IND.¹¹³

At this point, the drug begins a process of clinical trial that usually consists of three phases. The primary purpose of phase I trials is to determine how subjects tolerate, metabolize, and excrete the drug. The drug is administered usually to a few healthy subjects starting at low doses and gradually increasing to higher ones. If no adverse reactions occur, the drug moves on to phase II, where both safety and efficacy are determined. Phase II trials involve more subjects than phase I trials, and subjects have the disease the drug is designed to treat. The drug moves on to phase III once the drug's effective dose is determined and when no serious adverse reactions occur. Phase III trials involve hundreds or thousands of patients usually in the setting where the drug will eventually be used. The trials confirm the results of earlier studies and expand the knowledge about the drug. Before 1988, two clinical trials were typically required to show efficacy, but following amendments to the FD&C Act, the FDA may accept one clinical trial when there is other data corroborates the test results.¹¹⁴

After conducting the appropriate tests, the drug sponsor must submit to the Secretary of HHS a new drug application (NDA) containing:

(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug.¹¹⁵

Given the enormous amount of information required, NDA's typically consist of 2 to 15 volumes of summaries and 10 to 100 volumes of data. The FDA has 180 days to review the application to determine whether the

¹¹³See 21 C.F.R. §§ 56.103 & 312.66 (2004).

¹¹⁴See FDA, GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 3 (May 1998); Kulynych, *supra* note 109, at 129 (discussing the changes to the requirements for clinical evidence of effectiveness); *see also* 21 C.F.R. § 312.20 (2004) (describing the three phases of the clinical trial process); FROM TEST TUBE TO PATIENT, *supra* note 108, at 18 (generally describing the clinical trial process).

drug is safe and effective, whether it can be manufactured consistently, and whether the benefits of the drug outweigh the risks. Often the review takes longer, currently averaging 15.6 months.¹¹⁶ Once the drug's NDA has been approved, the manufacturer can begin marketing his drug. However, the manufacturer must still provide the FDA with prompt reports of serious adverse reactions and periodic reports of all information relating to safety and efficacy.¹¹⁷

Vaccines and other biologics must undergo a review process similar to that of new drugs. Current law prohibits the distribution of any biological product unless it has obtained a "biologics license."¹¹⁸ An application shall be approved once it is demonstrated that: (a) "the biological product that is the subject of the application is safe, pure, and potent" and (b) "the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent." The applicant must also consent to "the inspection of the facility that is the subject of the application."¹¹⁹ Although this statutory language differs from that covering new drug applications, the FDA has interpreted it to require the same amount and type of data as required for new drugs.¹²⁰ Hence, as with new drugs, the applicant must conduct animal and laboratory trials, submit an IND, and conduct clinical trials to establish safety and efficacy.¹²¹

Despite this similarity, the different historical evolution of biologics regulations and differences between biologics and other drug products have led to some different licensing requirements. Unlike new drugs, the safety and efficacy of biological products depends heavily on how they are made.¹²² Because of these differences, the FDA has imposed tighter controls on the manufacturing of biologics. These controls include a requirement

¹¹⁶ See *FDA's Drug Review and Approval Times*, at <http://www.fda.gov/cder/reports/reviewtimes/default.htm#FDA%20Review>.

¹¹⁷ See 42 U.S.C. § 355(k) (2004); 21 C.F.R. §§ 314.80 & 314.81 (2004).

¹¹⁸ See 42 U.S.C. § 262(a) (2004).

¹¹⁹ See 42 U.S.C. § 262(a)(2)(C)(i) & (a)(2)(C)(ii) (2004).

¹²⁰ See 37 Fed. Reg. 4004 (February 25, 1972); 42 U.S.C. § 262(j) (2004).

¹²¹ See *Consumer/Healthcare Information*, at <http://www.fda.gov/cber/faq.htm>.

¹²² See *How do biological products differ from conventional drugs?*, at <http://www.fda.gov/cber/faq.htm>; see also, *CBER's Recent Initiatives, Policies, and Inspections*, at http://www.fda.gov/cber/summaries/pda_japan1003jcp1.pdf.

that biologics manufacturers obtain licenses for each manufacturing facility making the product.¹²³ In addition, the FDA adopted a policy requiring the testing of each lot of vaccine prior to release.¹²⁴ Criticism that these requirements impose undue costs has led the FDA to remove the establishment license requirement¹²⁵ and to reconsider the lot release requirement for some biological products.¹²⁶

3. Improving Drug Approval

The approval process for a new drug involves a tradeoff between ensuring the safety and efficacy of marketed drugs and promoting the availability of new drugs. Increasing the number of studies required will minimize the risk that approved drugs are unsafe but will also delay the availability of potentially life-saving drugs. Higher regulatory hurdles may deter manufacturers from investing the time and money necessary to test a new product or submit the product for approval. As mentioned above, clinical testing imposes a significant portion of the direct costs of R&D. Long testing and review times also raise capital costs by distancing the time between the initial investment in R&D and the eventual payoff. Lowering these costs creates additional incentives for companies to develop new drugs, further increasing the availability of treatments for certain types of conditions.¹²⁷

In the late 1970's and early 1980's, the FDA emphasized the safety and efficacy side of this tradeoff, even when it meant withholding approval for potentially life saving treatments for terminally ill patients. The

¹²³ See Elimination of the Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products, 61 Fed. Reg. 24227 (May 1996) (hereinafter Elimination of the ELA).

¹²⁴ See 21 C.F.R. § 610.1 (2004); see also, Berkowitz v. U.S., 486 U.S. 531, 547 (1988).

¹²⁵ See Elimination of the ELA, supra note 123.

¹²⁶ See Interim Definition and Elimination of Lot-by-Lot Release For Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products, 60 Fed. Reg. 63048 (December 1995).

¹²⁷ Although the drug industry typically blames the FDA for the high costs of clinical testing, the FDA often reminds drug companies that regulatory standards are only one many factors contributing to high drug development costs. Drug companies often contribute to the problem by prematurely engaging in effectiveness trials or engaging in unnecessary trials to make the product more appealing to the ultimate consumer. See); Kulynych, supra note 109, at 129.

FDA's position has changed gradually since then. In the case of life threatening conditions, the FDA has given patients increased access to potentially life saving treatments in one of three ways. First, the FDA has given patients with serious diseases increased access to drugs that are still undergoing clinical investigation. Second, the agency has changed the clinical trial process to reduce the time and cost associated with the drug approval. Finally, the FDA has changed its management procedure to prioritize the review of NDA's for drugs that pose the greatest potential benefit to society. Overall, the institution of these policies demonstrates a change in the FDA's risk/benefit calculation and more fundamentally, in the agency's conception of the role it plays in drug development.

The FDA's early emphasis on safety and efficacy is exemplified by the case of *United States v. Rutherford*. In that case, terminally ill cancer patients sought access to an unapproved cancer treatment Laetrille.¹²⁸ They argued that the safety and efficacy requirements did not apply in the case of terminally ill patients and that there was no reasonable standard to measure safety and efficacy when a patient will likely die regardless of the therapy.¹²⁹ The FDA took the position that distribution of Laetrille was unlawful because no NDA had been submitted for the product. The outcome of the case confirmed the FDA's position. The Supreme Court unanimously held that the safety and efficacy requirements applied to all products, even those designed to treat terminally ill patients.¹³⁰ The court determined that FDA oversight was necessary because even terminally ill patients could be harmed by unsafe products.¹³¹

The Laetrile incident served to reinvigorate a long-standing controversy over the FDA's cautious approach to product approval. The FDA's caution is unsurprising. As mentioned above, the gradual expansion of

¹²⁸ See *United States v. Rutherford*, 442 U.S. 544, 548 (1979).

¹²⁹ See *id.* at 550-51.

¹³⁰ See *id.* at 558-59.

¹³¹ See *id.*

the FDA's powers generally occurred following well-publicized, national tragedies. As a result, the agency's history served to create a tradition that emphasized paternalism and safety over access to potentially life-saving therapies. As a result, the agency's role is conceived of narrowly as an agency whose sole purpose is risk prevention rather than an agency more broadly associated with drug development.¹³²

Political considerations may have also played a role in embedding risk-aversion at the FDA. Officials charged with approving or disapproving a new drug can make two different kinds of mistakes: (1) approving a drug that results in death or serious impairment; or (2) refusing to approve a drug that is capable of saving lives. While the costs of these errors appear compatible, victims of the first type of error are more readily identifiable and generate greater controversy than victims of the second type. As a result, FDA officials "will be led to reject or postpone approval of many a good drug in order to avoid even a remote possibility of approving a drug that will have newsworthy side effects."¹³³

Whatever the explanation for FDA's early risk aversion, the emergence of the AIDS crises "marked a seminal event in the evolution of new drug approval policy at the FDA."¹³⁴ AIDS patients employed grassroots tactics to protest FDA policies, including staging protests at the agency's headquarters.¹³⁵ Other groups of AIDS patients established a method whereby patients in clinical trials shared their active drugs with patients receiving placebos.¹³⁶ Other forms of civil disobedience included adding treatments prohibited by the IND protocol and developing a black market for drugs used in clinical trials.¹³⁷

While it is impossible to determine just how much these efforts influence decision making, FDA made

¹³²See Sheila R. Shuman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast Track Approval Initiatives: How Have They Worked?*, 50 Food & Drug L.J. 503, 517 (1995) (concluding that after the AIDS crises, "the agency's role has shifted from that of regulator to one of collaborator in the development and review process.")

¹³³Milton Friedman, *Newsweek*, January 8, 1973, at 582. See also, KIP VISCUSI, *THE ECONOMICS OF REGULATION AND ANTITRUST* 730-31 (3rd Ed. 2001).

¹³⁴Michael Greenberg, *Aids, Experimental Drug Approval, and the FDA Screening Process*, 3 N.Y.U. J. Legis. & Pub. Pol'y 295, 296 (1999/2000).

¹³⁵Nancy K. Plant, *Food, Allergy and the Health Care Financing Administration: A Story of Rage: Adequate and Well-Controlled Clinical Trials Reopening the Box*, 1 Wid. L. Symp. J. 267, 286 (1996).

¹³⁶*Id.*

¹³⁷See *id.*

numerous changes to its policies in the face of criticism from this politically organized and vocal group. The agency had long allowed for compassionate use IND exemptions that gave patients access to treatments still undergoing clinical trials.¹³⁸ However, these exemptions depended on the willingness of doctors to request the exemptions and of the drug manufacturer to provide drugs free of charge.¹³⁹ The large amounts of paperwork required and the lack of incentives for manufacturers made this process inadequate to meet the demand of AIDS patients.¹⁴⁰ In response, FDA updated these procedures informally, and in 1987, promulgated a final rule to formalize and update the process.

Under the final rule, seriously ill patients were granted access to new drugs when: (1) the drug is intended to treat a serious, or immediately life-threatening, disease; (2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (3) the drug is under investigation in a controlled clinical trial under an IND, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.¹⁴¹ Both physicians and the drug's sponsors were allowed to submit a protocol requesting the treatment use,¹⁴² and sponsors were allowed to charge for the use under certain conditions.¹⁴³ Although this "treatment IND" rule was intended in part to gain additional information on a drug's safety and efficacy, the primary purpose was "to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible."¹⁴⁴

Another procedure that increased the availability of drugs during early trials was the "parallel track" initia-

¹³⁸See Greenberg, *supra* note 134 at 315.

¹³⁹*Id.* at 316.

¹⁴⁰*Id.*

¹⁴¹21 C.F.R. § 312.34(b)(1)(i)-(iv) (2004).

¹⁴²21 C.F.R. § 312.35 (2004).

¹⁴³21 C.F.R. § 312.7 (d)(2) (2004).

¹⁴⁴21 C.F.R. § 312.34(b)(1)(i)-(iv) (2004).

tive. Meant specifically for patients with AIDS or HIV, the initiative makes promising investigational agents more widely available to patients who have no therapeutic alternative and who cannot participate in clinical trials.¹⁴⁵ Under this procedure, the FDA amends IND protocols for drugs that demonstrated promise in treating HIV and that appeared reasonably safe, taking into consideration the patient population.¹⁴⁶ Although similar in nature to treatment IND's, parallel track protocols were approved "when the evidence for effectiveness is less than that generally required for a Treatment IND."¹⁴⁷ Thus, the policy expanded access to AIDS drugs even earlier in the clinical trial process.

In addition to giving patients early access to treatments, the FDA also changed the clinical trial process to expedite the development and increase the availability of drugs used to treat serious ailments. In 1988, the agency issued an interim rule that allowed for the approval of life-saving drugs without the need for undertaking phase III trials.¹⁴⁸ This departure from the traditional structure of drug trials promised to create significant savings in time and money. This "expedited development" procedure had been based in part on the approval process for AZT, which had shortened by six years the time from initial human testing to final marketing approval of the drug. But expedited development process also creates the risk that patients will undertake unsafe or ineffective therapies. The FDA attempted to mitigate these risk through frequent meetings during phase I and II trials and by conducting post-marketing studies to obtain additional information about the product.¹⁴⁹ Although these procedures served to diminish some of the risks involved,

¹⁴⁵ See Final Policy Statement: Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Disease, 57 Fed. Reg. 13250 (April 15, 1992).

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ See 21 C.F.R. § 312.81 et seq. (2004)

¹⁴⁹ See 21 C.F.R. § 312.82 & 312.85 (2004) (discussing early consultation and phase IV trials). The FDA explained the purpose of early consultation when it issued the interim rule: "Most important, at the end of early (phase 1) clinical testing, FDA and the sponsor will seek to reach agreement on the proper design of phase 2 controlled clinical trials, with the goal that such research will be adequate to provide sufficient data on the product's safety and effectiveness to support a decision on its approvability for marketing." Interim Rule: Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses, 53 Fed. Reg. 41516 (1988). It also explained the importance of phase IV trials: "If FDA approval is gained on the basis of limited, but sufficient, clinical trials, it will usually be important to conduct postmarketing (phase 4) clinical studies that will extend the knowledge about the drug's safety and efficacy and allow physicians to optimize its use." *Id.*

the agency ultimately justified this new procedure by accepting that a different risk-benefit calculus would apply to products intended to treat seriously ill individuals.¹⁵⁰

Other changes to the clinical trial procedure occurred in 1992, when the FDA formalized a procedure that allowed the approval of drugs used to treat serious or life-threatening diseases based on data of “surrogate endpoints.”¹⁵¹ A surrogate endpoint is an indicator such as a clinical measurement or physical sign that is reasonably likely to predict a clinical benefit. Under the “accelerated approval” procedure, drugs for hypertension, for example, could be approved based on their effects on blood pressure rather than on survival or stroke rate.¹⁵² Because clinical benefits often took several years to manifest themselves, relying on surrogate endpoints served to shorten the clinical trial and reduce the time and costs for developing these types of drugs. Follow on studies were required to confirm the clinical benefits of the drug.¹⁵³

Finally, the FDA also changed its NDA review practice to prioritize review for those drugs that represent the greatest potential benefit to society. For AIDS drugs in particular, the agency created a new priority category, the AA category, to ensure that NDA’s for AIDS drugs received the highest priority review.¹⁵⁴ More generally, the FDA has created priority and standard review categories and instituted review procedures that direct attention and resources to highly-beneficial drugs.¹⁵⁵ FDA and independent studies confirm that the priority review category greatly reduces the time of NDA review. The FDA’s own study show that in the period from 1995 to 2000 standard review times vacillated between thirteen to about sixteen months while priority review time remained stable at about six months.¹⁵⁶ Importantly, because this change does

¹⁵⁰“The agency recognizes that safety and effectiveness are not absolute (i.e., not all drugs are free of risk or have unequivocal benefits), but must be assessed in light of what condition the drug treats. This is particularly true in the case of drugs to treat life-threatening diseases, where drugs that are quite toxic may nevertheless be considered safe under the circumstances.” *Id.*

¹⁵¹See 21 C.F.R. §314.520 (2004).

¹⁵²See Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942 (1992) (the comment noted surrogate endpoints had been used to approve these drugs prior to the rule).

¹⁵³*Id.*

¹⁵⁴See, FDA, *Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS* (March 5, 1998), at <http://www.fda.gov/oashi/aids/expanded.html>.

¹⁵⁵FDA CENTER FOR DRUG EVALUATION AND RESEARCH, MAPP 6020.3, REVIEW MANAGEMENT: PRIORITY REVIEW POLICY 2 (April 22, 1996), available at <http://www.fda.gov/cder/mapp/6020-3.pdf>.

¹⁵⁶See *FDA’s Drug Review and Approval Times*, *supra* note 116.

not tinker with the clinical trial process, it provides these benefits without significantly increasing the risk of approving unsafe or ineffective drugs.

Together, the procedures above fulfilled the goal of expanded access in several ways. By reducing time to approval and the investment necessary to get the drug to market, expedited development, accelerated approval, and priority review increase the prompt availability of life-saving drugs and created additional incentives for companies to invest in these products. One empirical study found that the regulatory phase for drugs initially approved under expedited review was 3.3 years, significantly less than for non-expedited drugs.¹⁵⁷ Similarly, the review time for AIDS drugs reviewed under expedited approval procedures averaged less than five months, substantially less than the fifteen months approval time for NDA review.¹⁵⁸ As a result, some industry analysts have predicted that pharmaceutical firms will intensify their efforts to research and develop treatments for serious diseases.¹⁵⁹ Treatment INDs and parallel track procedures have impacted drug availability in a different way. While not directly affecting the time or cost of clinical trials, these procedures increased the early availability of important new drugs in desperate situations by allowing their distribution while tests have occurred.

As noted above, the FDA realized that these procedures would sometimes create additional risks for patients. The course the FDA chose represented a significant departure from the agency's position in *U.S. v Rutherford*. By implementing these procedures, the agency demonstrated its willingness to allow patients in desperate situations to undertake greater risks. More fundamentally, these changes to FDA policy demonstrate how the agency has broadened its self-conception. The agency no longer focuses narrowly on preventing the approval of dangerous product but sees its mission as one that balances that concern within the broader

¹⁵⁷Shuman & Brown, *supra* note 132, at 513.

¹⁵⁸See Greenberg, *supra* note 134, at 324.

¹⁵⁹See *Biotech Firms to Boost Cancer Drug Level*, PHARMA MARKETLETTER, Feb. 2, 2004, at 0.

context of drug development.¹⁶⁰

Congress signaled its approval of these changes and urged continued innovation when it passed the Food and Drug Administration Modernization Act of 1997.¹⁶¹ In passing this legislation, one of Congress' central concerns was increasing prompt and efficient access to treatments. Several aspects of the legislation demonstrate this concern. The bill codifies FDA's mission as one that promotes the public health by, "promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."¹⁶² In addition, the bill's findings state that, "prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease."¹⁶³ Finally, statements during the bill's passage reaffirm Congress' concern with increasing access:

this bill sets up a new legislative and regulatory framework which reflects the latest scientific advancements. That framework continues the FDA's strong mission to public health and safety, but it sets a new goal for [sic.] FDA of enhancing public health by not impeding innovation or product liability through unnecessary red tape that only delays approval.¹⁶⁴

Then Secretary Shalala, while noting her concerns with specific provisions of the bill, agreed with the provisions updating the Agency's mission.¹⁶⁵

In order to achieve its goal of providing prompt and efficient access to treatment, the bill creates a Fast Track procedure for drug approval that basically codified many of the changes noted above. A drug can receive "fast track" designation if it was intended to treat a serious or life-threatening condition and it demonstrated the potential to address unmet medical needs.¹⁶⁶ The Secretary is required to "take such actions as are

¹⁶⁰ See Shuman & Brown, *supra* note 132, at 513; Plant, *supra* note 135, at 297.

¹⁶¹ See Food and Drug Administration Modernization Act of 1997, P.L. 105-115, 111 Stat. 2296 (November 21, 1997) (hereinafter FDAMA).

¹⁶² See 21 U.S.C. § 293(b)(1) (2004).

¹⁶³ See FDAMA, *supra* note 161, § 101(1).

¹⁶⁵ See *id.* at 9817.

¹⁶⁶ See 21 U.S.C. § 356(a)(1) (2004).

appropriate to expedite the development and review of the application.”¹⁶⁷ Fast Track designation provides a formal mechanism for sponsors to seek FDA input into development plans, and fast track products are often (though not necessarily) reviewed by expedited development (approval after phase II) and accelerated approval (approval based on surrogate endpoints) procedures. Like other provisions of the bill, this provision signaled Congress’s approval of the changes that had been occurring at the FDA.

4. Drug Approval and the Bioterrorist Threat

The regulatory and legislative changes above are helpful in considering the steps taken to address the emerging threat of bioterrorism. Using initiatives similar to the ones above, Congress and the FDA have updated the approval process for bioterrorism countermeasures to promote the development of these drugs and devices and to allow for earlier access to these products. As with other drugs, the decision to approve bioterrorism countermeasures presents a tradeoff between assuring the safety and efficacy of the drug or device and promoting the development of and access to new drugs. However, unlike drugs for AIDS, cancer, and other serious diseases, bioterrorist countermeasures do not treat significant current diseases. This small but significant difference creates particular hurdles for the development of many countermeasures and alters the risk-benefit calculation made by the FDA. As it did in the AIDS crises, the agency has become a collaborator in the development of these countermeasures rather than regulator of their approval. At the same time, because these new initiatives cannot be justified by the immediate need of patients suffering from serious or life-threatening diseases, the bioterrorist threat has pushed this role even further than before.

a. Accelerated Approval of Bioterrorist Countermeasures

¹⁶⁷*Id.* at § 356(a)(3).

The Public Health and Bioterrorism Preparedness and Response Act of 2002 helped to implement major changes to the approval process for countermeasures. One of the most important changes authorizes the Secretary of Health and Human Services, upon request of the product's sponsor, to designate a priority countermeasure as a fast track product and to give such products priority review designation.¹⁶⁸ As mentioned above, fast track designation provides a formal mechanism for sponsors to seek FDA input into development plans and provides sponsors with the option of requesting approval based on surrogate endpoints (accelerated approval) or after phase II clinical trials (expedited development).

The fast tracking of bioterrorism countermeasures represents an important departure from previous FDA policy. Fast tracking, accelerated approval, and expedited development were originally justified by the dire need of patients with serious conditions. The FDA recognized that these products may pose additional risks to patients, but stated that a different risk benefit calculus should apply in dire cases where no alternative therapy exists. The rationale for fast tracking and expediting the trial of AIDS and cancer drugs does not pertain to drugs used to treat outbreaks of bioterrorist diseases. Unlike AIDS and cancer, most of the diseases listed as bioterrorist threats do not currently affect many members of the population, and the current risk of a large-scale bioterrorist attack is not great. In these circumstances, the need for earlier approval of bioterrorist countermeasures is substantially less than the need for AIDS or cancer treatments, particularly because bioterrorist countermeasures can be approved on an emergency basis. In the bioterrorist context, the justification for accelerating approval of countermeasures rests more heavily on the incentives provided by the potential cost savings of fast track designation. This change in the justification for accelerating drug development pushes the FDA's role as collaborator in drug development further than before.

¹⁶⁸ See 21 U.S.C. § 356-1 (2004).

There are strong reasons to question whether this change is desirable, particularly if it leads the FDA to use accelerated or expedited approval. Without the current need for the treatment of bioterrorist diseases, the benefit of early access is clearly diminished. At the same time the departure from the traditional clinical trial process will create additional risks for the ultimate recipients of these products. As the FDA has noted, reliance on a surrogate endpoint creates additional uncertainty about a drug because endpoints may not be associated with the desired clinical benefit. In addition, long-term or serious health effects of a drug may not be recognized without large-scale or long-term clinical trials.¹⁶⁹

While the risks above pertain to all fast track products, the distinctive features of bioterrorist countermeasures make it even riskier to accelerate the approval of these products. Mistakes in the approval of a countermeasure could prove very costly during public health emergencies. The use of an unsafe or ineffective countermeasure during an emergency would likely create significant doubt over the government's ability to deal with the threat. At best, unsafe or ineffective countermeasures would multiply the psychological and emotional harm caused by an attack; at worst, they could lead people to panic. Unlike drugs currently approved under fast track procedures, some bioterrorist countermeasures cannot undergo non-clinical, post-marketing studies to further learn about the products safety and efficacy.¹⁷⁰ As a result, the safety and efficacy of some products may not be known until an actual emergency occurs.

While maintaining the traditional level of testing for countermeasures may increase the price tag for drug development, this reason alone should not justify designating all countermeasures as fast-track products.

The support for research and development for many of these products is heavily funded through government

¹⁶⁹See Lois K. Perrin, *The Catch-22 for Persons With AIDS: To Have or Not To Have Easy Access to Experimental Therapies and Early Approval For New Drugs*, 69 S. CAL. L. REV. 105 (1995).

¹⁷⁰Of course, the FDA could require phase III clinical studies after marketing, but this may lessen a sponsor's incentives to designate its product as a fast track product.

grants and contracts. As the FDA commissioner noted, “in some cases, [agencies at the government] have done the work to demonstrate safety and effectiveness of certain products for counterterrorism use, but we don’t yet have companies willing to produce these products.”¹⁷¹ Spending measures, such as grants, purchase contracts, or tax credits, could be used to promote the research and development of these products without compromising their safety. Even without such measures, because the government will likely be the greatest purchaser of some countermeasures, the price tag for these drugs likely will reflect the level of spending on research and development.

This discussion has avoided the debate over whether the FDA’s level of scrutiny is generally appropriate, and instead focused on the narrower issue of whether departure from the traditional clinical trial process is justified in this situation. A less stringent clinical trial process may be appropriate for AIDS or cancer treatments because of the current need for treatment. Even in these situations, however, commentators and members of the patient community have criticized accelerated approval mechanisms as subjecting the patient community to too much risk.¹⁷² Without the current need for treatment, the benefit of early access is considerably lessened. At the same time, less stringent procedures create additional risks to patients ultimately receiving these treatments.¹⁷³ In some respects, the risks of a mistaken approval are more significant for bioterrorist countermeasures than for other fast track products. The longer time available for the approval of bioterrorist countermeasures, the current availability of many treatments, and the possibility for emergency approval justifies greater caution in approving these drugs. For these reasons, fast track designation, accelerated approval, and expedited development should be used sparingly for those products that have the greatest current need taking into account the alternative therapies for bioterrorist diseases.

¹⁷¹See *Project Bioshield: Contracting for the Health and Security of the American Public*, Hearing Before the Committee on Government Reform, April 4, 2003 (statements of Dr. McClellan) (hereinafter “Bioshield Hearing”).

¹⁷²See *id.* at 140 (“The fact that some of the very groups that successfully lobbied for both easy access and early approval now desire to backtrack should send a warning to the FDA.”); Richard S. Nelson, *Regulation of Investigational New Drugs: Giant Step for the Sick and Dying?*, 77 GEO. L.J. 463, 484 (1988);

¹⁷³See Nelson, *supra* note 172, at 465 (noting that the approval of AIDS treatments involves a similar tradeoff between current availability and future risks).

b. The “Animal Rule”

A second provision of the Public Health and Bioterrorism Preparedness and Response Act calls on the FDA to pass the so-called “Animal Rule.” Proposed in 1999 and passed in 2002, the Animal Rule updates the clinical trial process by allowing some drugs to be approved based on efficacy studies conducted on animals rather than humans. These drugs would otherwise linger in the IND phase because approval would have required unfeasible or unethical clinical studies.

The regulation deals with another problem caused by the fact that many potential bioterrorist diseases do not affect a significant portion of the human population. Although clinical trial volunteers undertake greater risk when participating in tests for experimental drugs, their consent to this risk normally solves the ethical questions posed by human experimentation. Moreover, clinical tests to determine the efficacy of new drugs involve patients who already have the condition that the drug is intended to treat. However, in order to conduct human clinical tests of the efficacy of some biochemical countermeasures, volunteers would have to be exposed to agents that could cause serious morbidity or death. These volunteers would face not only the safety risk posed by the drug itself but also the significant risk of death or serious illness caused by deliberate infection by a life-threatening disease.

Deliberately exposing volunteers to life-threatening diseases would test the ethical boundaries of human experimentation. When making ethical judgments about human experimentation, there are at least two ethical values that come into play: the value of autonomy and the value of beneficence.¹⁷⁴ The value of autonomy is so fundamental to Western society that many sociologists speak of it as a religious principle.

¹⁷⁴See PAUL APPELBAUM, CHARLES LIDZ, ALAN MESIEL, *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE* 17 (1987).

In the words of one commentator, “the promotion of individualism in general and the development of each individual in particular has become the almost sacred task of the society as a whole and of its members.”¹⁷⁵ Given the special place of this principle in our society, it is not surprising that Western ethical systems see autonomy as a fundamental ethical value.¹⁷⁶ In the view of some ethicists, the value of autonomy becomes even more important in a society such as our own, where the exalted position of a few experts threatens the ideals of democracy and freedom by privileging the judgments of some persons over others.¹⁷⁷

Although autonomy is a fundamental value, it is not absolute. Western society and Western ethical systems also view the principle of beneficence (or, alternatively, the preservation of health) as a competing value when judging the appropriateness of human experimentation. The principle of beneficence imposes a moral obligation that society protect the well-being of its members and balance the risks and benefits involved in any action.¹⁷⁸ In the clinical context, for instance, the principle requires that drugs undergo animal testing before being given to humans. Beneficence can be understood as a sign of respect for humanity and as a prerequisite for personal satisfaction in human life.¹⁷⁹ Because of the historical paternalism of the medical profession, the principle of beneficence traditionally has more to do with biomedical ethics than the principle of autonomy, though the latter has resonance with “the individualistic temper of American life.”¹⁸⁰

The testing of biomedical countermeasures places these values in conflict by posing the question: should patients be allowed to consent to a process that will place their own health in serious jeopardy? Some ethical theorists have argued in other contexts that a rule prohibiting such consent unjustifiably privileges the principle of beneficence over the principle of autonomy by substituting the clinician’s own expert judgment

¹⁷⁵*Id.* at 26.

¹⁷⁶*See id.* at 27.

¹⁷⁷*See id.* at 28.

¹⁷⁸*See* THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT, at <http://www.fda.gov/oc/ohrt/irbs/belmont.html>.

¹⁷⁹*See* Appelbaum, *supra* note 174 at 29.

¹⁸⁰*See* Edmund D. Pellegrino, *The Metamorphosis of Medical Ethics: A 30 Year Retrospective*, in MARSHA GARRISON AND CARL E. SCHNEIDER, *THE LAW OF BIOETHICS: INDIVIDUAL AUTONOMY AND SOCIAL REGULATION* 12 (2003).

for that of the patient.¹⁸¹ In short, if sufficient patients voluntarily consent to exposure, no reason prevents such human clinical tests from taking place. This conclusion conforms with the more general observation that, “the principle of [autonomy] has tended in practice to dominate its fellows.”¹⁸²

Other commentators have argued that the principle of autonomy “is naïve, out of touch with an adequate understanding of human motivation, and, ultimately, philosophically and morally untenable.”¹⁸³ In the views of these commentators, autonomy has come to justify policies in situations where it could not possibly have any application.¹⁸⁴ On the other hand, in difficult situations (such as medically assisted suicide), these commentators point out how autonomy quickly falls by the wayside. Rather than admit that autonomy does not justify every decision, however, the courts often declare that the consent was not informed, knowing, or voluntary, even when there is substantial evidence to the contrary.¹⁸⁵ In fact, empirical studies of patients undergoing medical treatment generally have concluded that patients often do not wish to make medical decisions.¹⁸⁶ These studies call into question whether autonomy should be privileged over other values in making medical decisions.

While potentially controversial in theory, the conflict between autonomy and beneficence did not prove problematic in the debate over the regulation. Most comments to the proposed Animal Rule stated that it would never be appropriate to expose humans to disabling or lethal diseases. Agreeing with these comments, the FDA concluded, “it would be unethical to expose volunteers to potentially lethal or permanently disabling doses of toxic, biological, chemical, radiological, or nuclear substances to test the efficacy of products.”¹⁸⁷

¹⁸¹ See Robert Baker, *A Theory of International Bioethics: The Negotiable and the Non-Negotiable*, 8(3) KENNEDY INST. OF ETHICS J. 233, 258 (1998), citing TOM BEAUCHAMP AND JAMES CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* (1994).

¹⁸² See Garrison & Schneider, *supra* note 180 at 15.

¹⁸³ See Willard Gaylin, *Worshipping Autonomy*, 26 HASTINGS CENTER REPORTS 44 (November/December 1996), *quoted in* Garrison & Schneider, *supra* note 180 at 15. See also, WILLARD GAYLIN & BRUCE JENNINGS, *THE PERVERSION OF AUTONOMY* 185 (1996); Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 CATHOLIC LAW 455, 509 (1996).

¹⁸⁴ See GAYLIN AND JENNINGS, *supra* note 183, at 185.

¹⁸⁵ See Garnett, *supra* note 183, at 459.

¹⁸⁶ See Garrison & Schneider, *supra* note 180 at 85.

¹⁸⁷ See New Drug & Biological Products: Evidence Needed to Demonstrate the Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot be Conducted, 64 Fed. Reg. 53960, 53962 (October 5, 1999) (hereinafter Animal Rule).

Although lacking in theoretical exposition, the conclusion conforms with other legal documents that lay forth rules dealing with human medical experimentation.¹⁸⁸

After concluding that these experiments generally would be unethical, the FDA's final rule allows drug approval based on efficacy tests on animal species when these efficacy tests establish that the product is reasonably likely to provide the same clinical benefits in humans.¹⁸⁹ The rule only applies when unethical human studies would be needed to test efficacy; it does not apply to products that could be tested through field trials or that could be approved based on surrogate endpoints.¹⁹⁰ Because of its narrow scope, the rule is expected to apply only once every three years, so the risks of this change has been confined to only a small group of medicines.¹⁹¹ Nevertheless, as the FDA itself noted, drugs that are effective on animal species do not necessarily present the same benefits in humans. The FDA attempted to mitigate these risks by requiring that:

1. There is a reasonably well-understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product; 2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans; 3. The animal study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and 4. The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.¹⁹²

The animal rule demonstrates the agency's flexibility in dealing with new problems posed by bioterrorist

¹⁸⁸For instance, the Nuremberg Code on human experimentation states, "No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects." *Nuremberg Code on Human Experimentation*, at <http://www.med.umich.edu/irbmed/ethics/Nuremberg/NurembergCode.html>.

¹⁸⁹See 21 C.F.R. § 314.610 (2004).

¹⁹⁰See 21 C.F.R. § 314.600 (2004).

¹⁹¹See Animal Rule, *supra* note 187, at 53967.

disease. While the agency in general should attempt to achieve regulatory uniformity in the drug approval process, the significant ethical problem with human efficacy tests sufficiently distinguishes this category of drugs from others. Applying the traditional requirements for clinical trials to these drugs would likely prevent many of them from achieving final approval. Human efficacy tests would likely prove impractical not only because they would not attract sufficient volunteers but also because most IRBs would reject protocols that required such tests. More importantly, as evidenced by the comments to the rule, most persons would not find these tests ethically justified when non-clinical tests could provide scientifically comparable data. The question of consent to human experimentation is tied to the prior question of whether the research is necessary. Without the need to engage in morally questionable research, allowing patients to participate in studies does not demonstrate respect for the principle of autonomy, but simply uses patients as a means to satisfy curiosity. In utilitarian terms, the marginal benefit of human studies does not justify the significant risks to healthy volunteers.

The alternative – allowing these drugs to linger in IND status – would likely not solve the problem posed by these products. First, this solution only avoids the problem without changing any of the risks faced by the ultimate recipients of the drug. The Animal Rule at least mitigates these risks by imposing requirements designed to ensure that these drugs will have a similar effect in humans. Second, as will be discussed below, although the drug might be distributed under treatment INDs, obtaining informed consent from all recipients would likely prove cumbersome if not impossible. Hence, the approval of these kinds of drugs, based on adequate animal information and with appropriate disclaimers, proved to be the best solution in this situation.

c. Emergency Use Authorization

Project Bioshield, a more recent proposal, would authorize the distribution of unapproved countermeasures in the event of a public health emergency. The bill would allow the Secretary of Health and Human services to distribute countermeasures that have not achieved final approval when the Secretary of Homeland Security, the Secretary of Defense, or the Secretary himself declares that an actual or potential emergency threatens the civilian or military population.¹⁹³ To authorize the use of a particular product during a declared emergency, the Secretary must conclude:

- (1) The agent for which the countermeasure is designed can cause serious or life-threatening disease;
- (2) The product may reasonably be believed to be effective in detecting, diagnosing, treating, or preventing the disease;
- (3) The known and potential advantages of the product outweigh its known and potential risks;
- (4) There is no adequate alternative to the product that is approved and available; and
- (5) Any other criteria prescribed in regulation are met.¹⁹⁴

After making these determinations, the Secretary may authorize the distribution of drugs and prescribe conditions for their distribution. This proposal provides a flexible procedure to allow for the distribution of drugs after an outbreak of a bioterrorist disease. While the proposal represents an improvement over current alternatives, further amendments are required to further protect the rights of the ultimate recipients of these countermeasures.

The distribution of experimental new drugs for these purposes is currently governed by the treatment IND rules.¹⁹⁵ While these rules might also allow for the distribution of experimental drugs during a public health emergency, they were not developed to deal specifically with this threat. For this reason, the treatment IND rules have several disadvantages to the procedures proposed under the Bioshield Act. First, treatment INDs carry with them the connotation of experimentation, which is not only inappropriate when the drug is widely distributed but also potentially confusing to persons who are asked to undergo therapy. While

¹⁹³ See Project Bioshield Act of 2003, Discussion Draft, §4(b)(1), p. 37 (May 6, 2003).

¹⁹⁵ See 21 C.F.R. §§ 312.34 & 314.35 (2004).

the same may also be true for drugs currently distributed under treatment INDs, patients who currently receive these drugs already have some understanding of the drug approval process because of their disease. Stories of AIDS patients, for instance, suggest that they continually scan the press for articles about when experimental drugs become available.¹⁹⁶ Even if they do not have experience with the treatment IND rules, AIDS and cancer patients have the opportunity to discover more about the drug approval process and make informed decisions about the risks involved. In an emergency situation, persons asked to take a drug under a treatment IND will not have time and experience on their side, creating additional concern that they will not understand the meaning of treatment IND distribution.

Second, treatment IND rules provide no clear means to curtail lengthy informed consent procedures. Currently, exemptions to informed consent are allowed for emergency research or when obtaining informed consent is impractical and the risk to the subject is minimal. Neither of these exemptions is sufficient to deal with public health emergencies. The emergency research exemption does not allow an IRB to waive informed consent during an emergency but instead allows an IRB to approve an “investigation” without informed consent.¹⁹⁷ Because epidemiological studies could be used to test a widely-distributed product during an emergency, the term “investigation” could be strained to cover a product distributed during a public health emergency. However, this interpretation would likely be overreaching in light of the history of this regulation, whose express purpose is to permit “certain *adequate and well-controlled clinical trials* to occur that involve human subjects who are confronted by a life-threatening situation and *who also are unable to give informed consent because of their medical condition.*”¹⁹⁸ Hence, the emergency research exemption would likely not cover exemptions required by public health emergencies.

¹⁹⁶ See INSTITUTE OF MEDICINE, EXPANDING ACCESS TO INVESTIGATIONAL THERAPIES FOR HIV INFECTION AND AIDS 21 (Nat'l Academies Press 1991), available at <http://books.nap.edu/books/0309044901/html/21.html#pagetop>.

¹⁹⁷ See 21 C.F.R. § 50.24 (2004) (“The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained.”).

¹⁹⁸ See Final Rule: Protection of Human Subjects; Informed Consent, 61 FR 51498, 51498 (October 2, 1996) (emphasis added).

In addition, even if the emergency research exemption would apply to public health emergencies, the findings required by the regulation would not allow an IRB to grant a waiver of informed consent. Specifically, an IRB may only grant a waiver if it finds that the subject's medical condition makes obtaining informed consent unfeasible.¹⁹⁹ In a public health emergency, the feasibility of informed consent depends not on the subject's medical condition but on the conditions of hospitals, which are likely to be severely overwhelmed. Because the patient remains able to grant consent during an emergency, the IRB could not grant a waiver.

Other rules governing the research of human subjects provide different procedures for IRBs to grant waivers of informed consent. Under the federal policy on human research, an IRB may grant a waiver if: (1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.” While this appears to provide additional flexibility, the first and third requirements would make it difficult to grant waivers for countermeasures because use of a countermeasure may pose more than minimal risk and distribution does not truly involve research. For these reasons, physicians who administer drugs distributed under treatment INDs may still be required to provide patients with lengthy informed consent forms prior to administering treatment.²⁰⁰

Without the ability to obtain at least a partial waiver of informed consent, access to important treatments may be unnecessarily delayed by what may prove to be a symbolic rather than meaningful procedure. Under current rules, informed consent requires that each patient be given a statement that the study involves

¹⁹⁹See 21 C.F.R. § 50.24(a)(2)(i) (2004).

²⁰⁰The FDA may dispense with notice and comment rulemaking for “good cause,” such as when rulemaking would be impracticable or contrary to the public interest. See 5 U.S.C. §553(b)(B). However, expedited rulemaking after a public health emergency will not provide sufficient guidance *ex ante* and affords no opportunity for comment. If fact the government believes that emergency approval may some day be needed, it would be better to provide guidance before an emergency has occurred.

research; descriptions of any reasonably foreseeable risks, discomforts, or benefits; alternative procedures; confidentiality issues about the subject's medical records; explanation of compensation; treatments available for possible injuries arising from research involving more than "minimal" risk; and a statement that participation is voluntary and that the subject may discontinue participation without penalty.²⁰¹ Often these requirements translate into very long documents that may be quite cumbersome to read. Some empirical studies have concluded that under normal circumstances patients do not understand or recollect information given to them either orally from their physician or in a written consent form.²⁰² By multiplying these problems, a public health emergency diminishes the value of the informed consent process.

In addition, a public health emergency would multiply the problems caused by the time and effort required to administer informed consent. The smallpox vaccination program, conducted in 2002 by the CDC, illustrates some of the problems of conducting informed consent under a tight deadline. Producing the documents required for informed consent proved to be confusing and created difficulties for persons trying to implement the program.²⁰³ Although the procedures used to provide informed consent were abbreviated, the program nevertheless required participants to watch an informational video and complete multiple forms before being vaccinated.²⁰⁴ This process would be impossible to replicate during a public health emergency when hospitals are overcrowded and medical personnel are overwhelmed.²⁰⁵ In a true emergency, the time and effort spent on informed consent should be minimized to allow public health officials to focus on treating the sick.

At the same time, providing no information to patients regarding the risks of or alternatives to investigational drug treatments raises the specter of involuntary medical experiments such as the Tuskegee Syphilis Study,

²⁰¹ See 21 C.F.R. § 50.25(a) (2004).

²⁰² See Garrison & Schneider, *supra* note 180 at 113; Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 Am. J. L. and Med. 361, 385 (2002).

²⁰³ See GAO, GAO-03-578, SMALLPOX VACCINATION: IMPLEMENTATION OF NATIONAL PROGRAM FACES CHALLENGES 14 (April 2003).

²⁰⁴ See Holly A. Tailor and Ruth R. Faden, *Ethical Considerations in the Formation of a Smallpox Vaccine Policy*, 1 BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY, PRACTICE, AND SCIENCE 47, 51 (2003).

²⁰⁵ See Inglesby et al., *supra* note 55 (discussing "the crises at health care facilities").

the Jewish Chronic Disease Hospital case, or the Willowbrook State Hospital hepatitis study.²⁰⁶ These unfortunate incidents serve in part as reminders of the fundamental importance of autonomy in public health decisions. Even during times of emergencies, public health officials must respect individual risk preferences and the right to choose among available treatment options. One commentator has taken the stronger position that, “heightened respect should be shown for patient self-determination when the patient is in a life-threatening situation because this is, as a practical matter, the time when the patient’s preferences and value systems are likely to matter most.”²⁰⁷

The public has the right to expect candor from government officials particularly during times of crises. A decision by DHHS to approve an experimental treatment during an emergency could prove disastrous to the government’s legitimacy if the department does not provide the public with information regarding the treatment. The distrust that such a decision would engender may also create a practical barrier to dealing with the emergency because victims may no longer trust the instructions given to them by government officials. A decision to curtail informed consent should guard against overreaching and should be narrowly tailored to the emergency.

By providing clearer authority and greater flexibility to curtail informed consent, Bioshield provides a necessary change to current rules in the unlikely but potential event of a bioterrorist attack. In some ways, however, the proposal goes too far. While the bill generally requires that the Secretary inform end users of the benefits of, risks of, and alternatives to the experimental treatment, the Act also allows the Secretary to curtail disclosure to patients so long as the Secretary determines that providing information is not “feasible given the circumstances of an emergency.”²⁰⁸ This discretionary power, already quite broad, is broadened

²⁰⁶For a brief history of these experiments, see BARRY R. FURROW, ET. AL., HEALTH LAW 979 (2000).

²⁰⁷See Richard S. Saver, *Critical Care Research and Informed Consent*, 75 N.C.L. REV. 205, 253 (1996).

²⁰⁸See Project Bioshield Act of 2003, Discussion Draft, § 564(c)(1)(A)(ii).

further by the definition of “emergency,” which includes both actual public health emergencies and potential civilian or military emergencies.²⁰⁹ In all likelihood, some form of disclosure (perhaps even full informed consent) would remain feasible during a potential civilian emergency. However, in the context of potential military emergencies, the Secretary could determine that preparations for war make it unfeasible to provide disclosure to members of the armed forces. Under current statutes and regulations, only the President can waive prior consent requirements for members of the military, and the Department of Defense must obtain independent IRB review of the proposed waiver and must provide service members with a written information sheet about the drug.²¹⁰ Without further specifying when a waiver is appropriate, the proposed bill could be used to circumvent these safeguards.²¹¹

In addition, Project Bioshield provides no opportunity for public comment regarding the substance of a waiver or the procedures used to obtain them. Other legislation allowing waivers of informed consent requires that the agency pass appropriate regulations governing such waivers.²¹² This procedure allows the public to provide its opinions regarding waivers of consent and usually result in regulations that provide specific guidance on how to obtain a waiver and when waivers are appropriate. Clearly, rulemaking would not be appropriate after an actual emergency has occurred, but the public should be allowed to participate in rulemaking prior to emergencies to influence how and when the secretary should grant waivers.

The resulting rules would likely provide more meaningful safeguards than the current bill, which leaves much to the discretion of the Secretary. As mentioned above, regulations governing waiver of consent for military

²⁰⁹ See Project Bioshield Act of 2003, Discussion Draft, § 564(b)(1) (the definition of emergency includes “significant potential for a national [or military] emergency, involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent.”).

²¹⁰ See *id.* at § 50.23(d)(1)-(4).

²¹¹ See 21 C.F.R. § 50.23 (2004).

²¹² See 21 U.S.C. § 355(i) (2004).

personnel require third party review before a waiver is authorized. Regulations governing emergency room research provide specific guidance to determine when informed consent is feasible. Regulations could provide similar guidance for waivers during public health emergency. The procedures for emergency authorization should distinguish actual emergencies from potential ones, and provide different powers and procedures for each situation. The discretion to authorize emergency use of a product should also depend on the extent of testing that the product has undergone. Products still in phase I clinical trials pose a considerable risk to the lives of individuals. Statisticians explain that even if no serious toxicities are observed in a phase I clinical trial involving twenty patients, as many as one in six people could experience severe toxic reactions were the drug distributed.²¹³ More specific guidance is needed to distinguish products on the basis of the amount of testing that the product has undergone.

A final problem with the procedures proposed by Project Bioshield has to do not with informed consent but with the potential abuse by manufacturers of the drug. Without the possibility for emergency approval of their products, manufacturers have the incentive to pursue accurate and immediate testing of investigational new drugs. These incentives diminish with the possibility that investigational drugs will be widely distributed without the need for conducting clinical trials.²¹⁴ Of particular concern are those drugs whose only potential use is the treatment of a bioterrorist disease because the market for these drugs will only arise in the event of an attack.

To solve the analogous problem created by treatment INDs, regulations require that manufacturers of those drugs pursue FDA approval with “due diligence.” Unfortunately, the regulation has proven ineffective because the vagueness of its language makes it difficult to apply and because the FDA has the burden

²¹³See INSTITUTE OF MEDICINE, *supra* note 196, at 28.

²¹⁴See also Nelson, *supra* note 172, at 484 (arguing that similar disincentives may occur because of treatment INDs).

of proving lack of diligence.²¹⁵ A more effective solution would require that drugs subject to emergency authorization follow an objective timetable for clinical testing.²¹⁶ Current regulations require that IND holders to file annual reports regarding the status of drug development, but they do little to ensure that manufacturers pursue research diligently. Regulations imposing time limits and penalties may spur drug manufacturers to timely pursue drug development. While monetary fines might eventually be (partially) passed on to consumers in the form of higher prices, Congress could allow the FDA to penalize companies by shortening the patent term for a drug by an amount of time equal (in value or days) to the delay. However, this penalty is worrisome because it could reduce the incentive to pursue clinical trials to completion.

While these alternatives would require amendments to the FD&C, for many bioterrorist countermeasures, the solution could be implemented through contracts for the development of these new drugs. These contracts between the government and drug developers could establish timelines for clinical tests and establish penalties for non-completion. Moreover, to the extent that contracts for the purchase of countermeasures will only pay out when drugs have achieved full approval, the drug manufacturer has added incentive to diligently pursue drug testing. Together, the push of regulations and the pull of these incentives may provide for timely testing of countermeasures.

With further amendments, Project Bioshield would appropriately balance the value of additional flexibility with the safeguards needed to prevent overreaching. While distributing unapproved products potentially poses substantial risks, some authority to distribute investigational drugs and curtail informed consent procedures is desirable in the event of a dire public health emergency. The FDA has previously stated that it may be impossible to obtain informed consent in emergency situations and that it is currently difficult and controversial to grant such waivers.²¹⁷ By providing for additional authority to exempt cumbersome informed consent procedures during an emergency, the Bioshield proposal provides a substantial advantage

²¹⁵ *See id.*

²¹⁶ *See id.*

²¹⁷ *See* Animal Rule, *supra* note 187, at 53963.

over treatment INDs. In some respects, however, the proposal goes too far.²¹⁸ Specifically, the legislation (through notice and comment regulation) should provide clearer protection for informed consent during an actual or potential emergency, and it should guard against the possibility that drugs subject to emergency use approval will linger in the IND phase.²¹⁹

C. Conclusion: Looking Forward to New Initiatives

The initiatives described above represent only a few of the numerous proposals that address the growing need for treatments not just for bioterrorism but for other public health emergencies. There are many proposed changes on the horizon that will affect the propriety of the initiatives discussed above. In particular, liability protection, the availability of compensation, the right to grant compulsory licenses of patents in emergencies, and the FDA's ability to enforce post-marketing studies of drugs all play an important role in evaluating the changes meant to deal with the terrorist threat.

Drug companies have repeatedly called for liability protection for drugs developed to treat chemical and biological agents.²²⁰ Imposing liability on a manufacturer after the emergency distribution of an unapproved product may be unfair to companies manufacturing needed treatments. More importantly, liability protection for countermeasures may provide additional stimulus for the development of these products, particularly for small pharmaceutical companies who are especially sensitive to liability. Exposure to liability has already caused many vaccine manufacturers to exit the vaccine market, producing what many consider a crisis in the

²¹⁸ *Accord Bioshield Hearing, supra* note 171, at 8 (Comments of Congressman Waxman).

²¹⁹ *See also, Hearing on Project Bioshield Before the House Committee of Energy and Commerce*, March 27, 2003 (statements of Dr. Christensen) (“In the interest of protecting the public, wouldn't it be best for us in this bill to require a contract for the procurement of a countermeasure to include a term that the product vendors seek FDA approval even after that emergency approval and that the licensing or clearance for the product and a time table for development of that approval be included in that contract.”).

²²⁰ *See Bioshield Hearings, supra* note 171, at 117 (statements of Dr. Friedman).

vaccine industry. While it may be too early to tell whether the industries' are analogous, a similar situation could occur in the field of countermeasure production.

Some policymakers have questioned whether liability protection is appropriate or even necessary. Despite the uncertainty of bioterrorist attacks, insurance may be available for many countermeasures.²²¹ Moreover, companies already have some form of liability protection through the government contractor defense and the Support Anti-Terrorism by Fostering Effective Technologies (SAFETY) Act. The former shields contractors from tort liability for products manufactured for the Government in accordance with Government specifications, if the contractor warned the United States about any hazards known to the contractor but not to the Government.²²² The latter applies a series of restrictions (on damages, for instance) and other special rules to lawsuits against sellers of a product that have been qualified by the Secretary of Homeland Security as "qualified anti-terrorism technology."²²³ Critics worry that shielding manufacturers from liability lessen the incentives to adequately test drugs before marketing them. The desirability of liability protection must be considered in light of the changes to the clinical trial process that occur at the FDA.

Closely related to the issue of liability protection is the issue of victim compensation.²²⁴ In general, victims of unsafe or ineffective treatment rely on insurance and lawsuits to obtain compensation for their injuries. In response to the uncertainty and high costs of toxic tort cases, Congress has created several programs to provide no-fault compensation through an administrative system that is less costly than mass toxic tort

²²¹ See *In re Novavax, Inc.*, File No. B-286167, GAO Decision, December 4, 2000 (two of four companies submitting a bid to a government contract for the development and stockpiling of smallpox vaccine were able to get insurance indemnifying the government for any claims or costs resulting from clinical trials, use in immuno-compromised individuals and pregnant women, and use in emergency situations).

²²² *Hercules Inc. v. United States*, 516 U.S. 417, 422 (1996).

²²³ See Julie Samia Mair and Michael Mair, *Vaccine Liability in the Era of Bioterrorism*, 1(3) BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY 169, 172 (2003).

²²⁴ Compensation initiatives are often tied to liability protection, though the government could provide victim compensation without altering manufacturer liability.

suits.²²⁵ In the view of some ethicists, the availability of compensation would make it not only morally permissible but morally obligatory to dispense with ordinary informed consent requirements after an attack.²²⁶ The Project Bioshield proposal, however, does not provide any mechanism to compensate persons injured by a product leased through emergency authorization. The addition of victim compensation provides additional moral justification for curtailing informed consent and will help in healing the national trauma of an attack.²²⁷

Aside from the issue of liability and compensation, other proposals have focused on the effect of the patent system on the government's ability to provide countermeasures during an emergency. A manufacturer of patented drug may not be able to keep up with the increased demand for a product following an attack. This effect already has occurred in the wake of the anthrax scare when the demand for CIPRO quickly outpaced the ability of the patent holder, Bayer, to produce the drug.²²⁸ As a result, members of Congress have proposed legislation that will allow companies other than the patent holder to manufacture a product in response to an attack.²²⁹ The proposal clarifies the government's right to grant compulsory patent licenses and provides a method for establishing a reasonable royalty for the use of a patented product. Other proposals require that drugs developed with funds from the NIH must be reasonably priced. While the potential for compulsory licensing may create a disincentive for pharmaceutical companies to develop and

²²⁵For example, Congress has created the National Vaccine Injury Compensation Program to provide liability protection and compensation for injuries or death resulting from a qualifying childhood vaccine. See 42 USCS §§ 300aa-10 through 34 (2004). Congress has also provided liability protection and compensation for injuries arising out of the National Smallpox Vaccination Program. See Homeland Security Act of 2002, Pub. L. No. 107-296, Title VIII, Subtitle G, §§ 861-865, 116 Stat. 2238-2241 (Nov. 25, 2002) (codified at 6 USCS §§ 441-444); Regulations Implementing the Support Anti-Terrorism by Fostering Effective Technologies Act of 2002 (The SAFETY Act); Proposed Rule 68 Fed. Reg. 41420 (July 11, 2003). The controversial September 11th Victim's Compensation Fund is yet another example.

²²⁶See Ruth R. Faden, Holly A. Taylor, and Naomi K. Seiler, *Consent and compensation: a social compact for smallpox vaccine policy in the event of an attack*, 36 CLIN. INFECT. DIS. 1547-51 (2003).

²²⁷See *id.* The authors argue that patients should not be required to pay for the adverse reactions caused by countermeasures, but they do not discuss who should pay for the harm or how to avoid passing the costs on to patients.

²²⁸See Alfred B. Engelberg, *Increasing Access to CIPRO: A Strategy for Rapid Creation of a Government Stockpile*, a memo to Senator Schumer, October 13, 2001, available at <http://lists.essential.org/pipermail/ip-health/2001-October/002113.html>; Christopher K. Eppich, *Patenting Dilemma: Drugs for Profit Versus Drugs For Health*, 43 Santa Clara L. Rev. 289 (2002).

²²⁹See Affordable Prescription Drugs and Medical Inventions Act, 107 H.R. 1708 (2001).

produce countermeasures, the substantial government investment in biodefense (both in terms of research grants and purchasing contracts) and the availability of a reasonable royalty to patent holders pushes the incentives in the other direction. At the same time, the ability to quickly fill shortages of a product during a public health emergency is crucial. Congress should carefully consider compulsory license and reasonable price provisions in order to provide sufficient quantity of a product during public health emergencies.

Finally, post-marketing studies become particularly important for countermeasures approved with accelerated procedures or after animal trials. Past experience has shown that manufacturers often fail to conduct the studies required of them and that the FDA lacks the ability to monitor studies or the power to require them. For instance, the FDA previously has declined to sanction drug sponsors for failure to complete post-marketing studies of AIDS treatments approved using accelerated procedures.²³⁰ Although the FDA may withdraw conditional approval when sponsors fail to satisfy post marketing study requirements with due diligence,²³¹ the unpopularity of removing drugs from the market has prevented them from applying this rule. To solve this problem, the FDA should withhold final approval until manufacturers submit postmarketing study protocols, and the agency or congress should assert the authority to impose monetary or criminal sanctions on drug sponsors who fail to comply with postmarketing study requirements.²³² The FDA might also be authorized to sanction companies by curtailing patent terms or protection.

As the agency that approves drug products used to treat bioterrorist diseases, the FDA plays a significant role in the domestic preparation against a bioterrorist attack. The significant changes that occurred at the FDA in response to the AIDS crises have created an agency culture willing to accept a role as collaborator in the lengthy and expensive process of drug development. These changes have set the scene for and prepared

²³⁰Perrin, *supra* note 169, at 136 & 139.

²³¹21 C.F.R. § 314.530 (2004).

²³²*See also*, Perrin, *supra* note 169, at 152 (discussing similar proposals for AIDS and cancer drugs).

the agency to deal with the problems posed by bioterrorism countermeasures. In some ways, however, the initiatives meant to address the bioterrorist threat have pushed the agency's role as collaborator even further than before.

Many of the proposals meant to deal with the AIDS and cancer crises in the 1980's and 90's have been altered and reapplied to the problems posed by bioterrorist diseases. Like drugs for AIDS and cancer, countermeasures can be designated as fast track products and are subject to accelerated approval and expedited development. In addition, countermeasures will soon be subject to emergency approval procedures analogous to but more flexible than treatment INDs. Finally, some countermeasures can be approved or distributed on the basis of efficacy tests conducted on animals only. Like the initiatives introduced to deal with AIDS and other serious diseases, these changes provide earlier access to treatments in time of need and accelerate the development and approval of countermeasures for bioterrorist diseases.

Despite the public fear of the risks of a bioterrorist attack, policymakers must keep in mind the current nature of the threat when proposing measures that could curtail the future safety of the victims of a public health emergency. The fast track procedures currently in place do not necessarily lead to less stringent testing of drug products, but the ability to designate countermeasures as fast track products may lead the FDA to approve these products after curtailed or accelerated clinical tests. Where people are not currently dying from bioterrorist diseases, the balance of risks and benefits that justify less stringent testing for AIDS and cancer treatments does not apply to bioterrorist countermeasures. Because of the additional risks of less stringent testing – some of which are peculiar to countermeasures – countermeasures should receive the same rigorous testing as required for other products, particularly when countermeasures could be approved if and when an emergency so warrants.

At the same time, the FD&C should not be a death pact. The uncertainty of the bioterrorist threat requires sufficient flexibility to ensure that agencies have the appropriate authority to deal with the unlikely but potentially devastating event of a bioterrorist attack. The animal rule and the proposal for emergency authorization provide the means to distribute drugs that may be needed in times of emergency. With additional amendments, they will also provide adequate protections for the rights of the recipients of these treatments.